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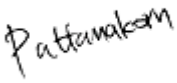
Declaration

This work is original and has not been submitted previously in support of a degree qualification or other course.

Signed: 

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List of Abbreviations

$(a-\bar{v})O_2$ diff - Arteriovenous oxygen difference

AACVPR - American Association of Cardiovascular and Pulmonary Rehabilitation

ACPICR - Association of Chartered Physiotherapists in Cardiac Rehabilitation

ACSM - American College of Sports Medicine

ANS - Autonomic nervous system

BACPR - British Association for Cardiovascular Prevention and Rehabilitation

BMD - Body bone mineral density

BMI - Body mass index

CAV - Cardiac allograft vasculopathy

CINAHL - Cumulative Index to Nursing and Allied Health Literature

CMIT - Continued moderate-intensity training

CMV - Cytomegalovirus

CPX - Cardiopulmonary exercise

CR - Cardiac rehabilitation

CT - Continuous training

CVD - Cardiovascular disease

EDA - End-diastolic cavity area

EDV - End-diastolic volume

EDVD - Endothelial-dependent vasodilation

EF - Ejection fraction

eGFR - Estimated glomerular filtration rate

EIVD - Endothelial-independent vasodilation

EnF - Endothelial function

ESA - End-systolic cavity area

ESV - End-systolic volume

ET - Exercise training

HF - Heart failure

HHT - Heterotopic heart transplantation

HIIT - High-intensity interval training

HR - Heart rate

HRQoL - Health-related quality of life

HTRs - Heart transplant recipients

HTx - Heart transplantation

ISHLT - International Society for Heart and Lung Transplantation

IT - Interval training

KTRs - Kidney transplant recipients

LTM - Lean tissue mass

LV - Left ventricular

MET - Metabolic equivalent

NS - Not stated

NYHA - New York Heart Association

OHT - Orthotopic heart transplantation

PEDro - Physiotherapy Evidence Database

PHT - Pulmonary hypertension

PO - Power output

$\dot{Q}$ - Cardiac output

QOL - Quality of life

RCT - Randomised controlled trial

RER - Respiratory exchange ratio

RM - Repetition maximum

RPE - Rating of perceived exertion

SBP - Systolic blood pressure

SV - Stroke volume

UCT - Uncontrolled trial

$\dot{V}_E$ - Minute ventilation

$\dot{V}_E / \dot{V}_{CO_2}$ - The minute ventilation/carbon dioxide production

$\dot{V}_{O_2}$max - Maximal oxygen consumption

$\dot{V}_{O_2}$peak - Peak oxygen consumption

Literature review

1. Abstract

Heart transplantation (HTx) not only reduces mortality of patients with end-stage heart failure (HF), but also improves the quality of life of these patients. However, heart transplant recipients (HTRs) experience a decrease in exercise capacity, which is associated with increased mortality of cardiovascular patients. This literature review provides not only the basic clinical application of HTx, such as recipient selection and surgical techniques, but also unique physiological abnormalities after surgery. Factors that are related to chronotropic incompetence, side effects of immunosuppressant medications, and deconditioning result in decreased exercise performance in HTRs. The benefits of exercise-based cardiac rehabilitation (CR) are outlined in this literature review. Exercise training (ET), which consists of aerobic, resistance and flexibility exercises, is effective in improving peak oxygen consumption ($\dot{V}O_2$peak) and skeletal muscle performance in HTRs. There is evidence that the use of high-intensity interval training (HIIT) can improve chronotropic responses to exercise and reduce the progression of cardiac allograft vasculopathy (CAV), which limits long-term survival rates in HTRs. Finally, it should be noted that the normal ageing process may affect long-term outcomes of ET in HTRs.

2. Introduction

HTx is recommended as the gold standard treatment for selected people with refractory end-stage HF (Yancy et al., 2013). After surgery, patients undergoing HTx have improved health-related quality of life (HRQoL) (Grady et al., 2007; Grady, Jalowiec, & White-Williams, 1996; Mantovani et al., 2016). HTx has also been widely accepted as a life-prolonging treatment (Schroeder, Moffatt, Berry & Robbins, 2004) and it can effectively decrease mortality of high-risk patients with advanced HF (Deng, De Meester, Smits, Heinecke, & Scheld, 2000). Since the only 18-day survival of the first human HTx in 1967 (Brink & Hassoulas, 2009), currently, the median survival period of adult HTRs is 10.7 years, according to the International Society for Heart and Lung Transplantation (ISHLT) Registry data (Lund et al., 2017).

Although post-transplant survival has increased due to advances in HTx procedures, including surgical techniques, criteria for HTx candidates, and immunosuppressive medications to control allograft rejection (Lund et al., 2017), exercise capacity and HRQoL of HTRs remain lower than their normal counterparts (Anderson et al., 2017).

A unique physiology due to complete denervation of the transplanted heart (Hunt, 1998) is associated with exercise intolerance in HTRs (Keteyian, 2013; Silva & Cipriano, 2016). Moreover, negative side effects of lifetime immunosuppressive drug therapy not only cause infections, which are the leading cause of death in the first year after HTx (Colvin et al., 2018; Lund et al., 2017), but are also the possible causes of CAV (Keteyian, 2013; Silva & Cipriano, 2016), which remains a crucial problem that limits long-term survival rates in HTRs (Colvin et al., 2018; Hunt, 1998; Lund et al., 2017).

CR has been shown to reduce morbidity, mortality, hospital admissions, and to improve quality of life (QOL) as well as psychological well-being in individuals diagnosed with cardiovascular disease (Dalal, Doherty, & Taylor, 2015). The British Association for Cardiovascular Prevention and Rehabilitation states that HTRs also benefit from CR (BACPR, 2017). Early provision of CR or secondary prevention programmes to all HTRs has been recommended in international guidelines (Thomas et al., 2010). However, many guidelines for HTRs mainly focus on exercise rehabilitation (American Association of Cardiovascular and Pulmonary Rehabilitation [AACVPR], 2013; American College of Sports Medicine [ACSM], 2018) because improving exercise capacity has been highlighted as an important goal to prolong the life of the individual (Silva & Cipriano, 2016) due to a decrease in mortality rates, as reported by Myers et al., (2002).

This review provides the basic clinical application of HTx, including patient selection, surgical techniques and immunosuppressant therapy, physiological changes, complications and exercise performance after HTx, and exercise-based CR for HTRs and its benefit.

3. Heart transplantation

3.1 Recipient selection

Although HTx is known as an effective treatment for individuals with end-stage HF with reduced ejection fraction (Katz, Waters, Hollis, & Chang, 2015), this procedure is recommended for eligible patients who meet the criteria as outlined in Table 1 (De Jonge et al., 2008; Deng, 2002; Dennell, 2009; Hunt & Frazier, 1998; Isaac et al., 2011; Katz et al., 2015; Mehra et al., 2006).

Table 1 Indications (A.) and contraindications (B.) for heart transplant candidates

A. Indications

- End-stage heart failure
- Refractory life-threatening arrhythmias despite optimal medication, surgical, and device therapy
- Refractory angina not amenable to further revascularisation
- CPX testing: $\dot{V}_{O_2}$peak ≤14 ml/kg/min or ≤12 ml/kg/min if on betablockers or high risk of the Heart Failure Survival Score with borderline $\dot{V}_{O_2}$peak
- Severe ventricular dysfunction (EF <20%) with NYHA Class III-IV despite optimal medical and device therapy

$\dot{V}_{O_2}$peak, peak oxygen consumption; CPX, cardiopulmonary exercise; EF, ejection fraction; NYHA, New York Heart Association

B. Contraindications

Absolute contraindication	• Active neoplasm from origins other than skin • Severe symptomatic cerebrovascular or peripheral vascular disease • Active systemic infection such as HIV • Active substance abuse
Relative contraindication	• Age >70 years old • BMI >30 kg/m^2 • Diabetes with end-organ damage or poor glycaemic control (HbA1c >7.5) despite optimal effort • Severe PHT/ elevated pulmonary vascular resistance • Irreversible renal dysfunction (eGFR <40 ml/min) • Active tobacco smoking during the previous 6 months • Mental retardation or dementia • Poor compliance with medical regimens
May consider multi-organ transplantation	• Severe dysfunction of other organs such as lung, kidney and liver

BMI, body mass index; eGFR, estimated glomerular filtration rate; PHT, pulmonary hypertension

There is no single test or measurement to determine patients for HTx (Hunt & Frazier, 1998). Although a CPX test is currently accepted to indicate transplant listing (Mehra et al., 2006), a combination of clinical assessment and functional status is also needed (De Jonge et al., 2008; Isaac et al., 2011; Katz et al., 2015). Patients with >70 years of

age or comorbidities, including obesity, diabetes, HIV, active malignancy and severe cerebrovascular disease, as well as a psychosocial status that interferes with the patient's ability to adhere to a long-term medical regimen are considered as contraindications to HTx (see Table 1B) (De Jonge et al., 2008; Isaac et al., 2011; Mehra et al., 2006). Such contraindications may lead to poor prognosis for survival or poor QOL of HTRs (De Jonge et al., 2008; Mehra et al., 2006). Therefore, for the greatest outcomes of HTx, it is important to apply those criteria (see Table 1) to all HTx candidates.

3.2 Surgical techniques

I. Orthotopic heart transplantation

There are three techniques for orthotopic HTx (OHT), as shown in Table 2 (Antretter & Laufer, 2001).

Table 2 Orthotopic heart transplantation techniques

Orthotopic heart transplantation	**Anastomosis**
Biatrial (standard) technique	Left atrium, right atrium, pulmonary arteries and aorta
Bicaval technique	Left atrium, superior vena cava, inferior vena cava, pulmonary arteries and aorta
Total technique	Right-sided left Atrial Cuff, left-sided left Atrial Cuff, superior vena cava, inferior vena cava, pulmonary arteries and aorta

By using anastomoses at the mid-atrial levels, the standard biatrial procedure can cause atrial geometry abnormality, resulting in post-transplant complications, including atrial arrhythmias, atrioventricular valve insufficiency, tricuspid and mitral valve regurgitation (Antretter & Laufer, 2001). Because of this, the bicaval and total techniques have been developed in an attempt to avoid such problems by altering

anastomoses (see Table 2). However, a literature review that compared these three OHT techniques found that the bicaval technique had the greatest benefits, including improved survival and atrial geometry in addition to a decrease in atrioventricular valvular insufficiency, arrhythmias, pacing requirements, vasopressor requirements, and hospital stay (Morgan & Edwards, 2005).

II. Heterotopic heart transplantation

Heterotopic HTx (HHT) is performed by connecting the donor heart in parallel with the recipient heart to function as a biological biventricular support (Flécher et al., 2013). HHT is useful for fixed PHT patients in addition to reduced incidence of hypertension (Flécher et al., 2013).

According to advances in immunosuppression and mechanical circulatory support, the use of HHT is less than in the past (Flécher et al., 2013). The bicaval OTH procedure has been the preferred technique in many transplant centres globally (Dennell, 2009).

3.3 Immunosuppressant medications

To control the destruction of the allograft (i.e. allograft rejection), resulting from the recipient's alloimmune response (Deng, 2002), immunosuppressive therapy is needed (Deng, 2002; Silva & Cipriano, 2016). However, adverse side effects of immunosuppressant medications, such as infections, muscle atrophy, myopathy, osteoporosis, renal dysfunction, diabetes and the possible CAV, should be considered (Silva & Cipriano, 2016). Table 3 shows commonly used immunosuppressant drugs and their major adverse side effects (Deng, 2002; Silva & Cipriano, 2016).

Table 3 Commonly used immunosuppressant agents and their major side effects

Drug	**Main side effects**
Corticosteroids (Prednisone)	Fluid retention, muscle atrophy, myopathy, osteoporosis, psychosis
Azathioprine	Marrow suppression, hepatopathy
Cyclosporine	Hyperglycaemia, hypertension, nephrotoxicity, electrolyte abnormalities
Tacrolimus	
Mycophenolate mofetil	Hyperglycaemia, hypercholesterolaemia, hypertension, peripheral oedema
Polyclonal antithymocyte globulin	Infection, malignancies
Monoclonal CD3 antibodies	
Sirolimus	Hypertriglyceridemia, hypercholesterolaemia, hypertension, peripheral oedema
Everolimus	

3.4 Physiology in the early post-heart transplantation

I. Denervation of the transplanted heart

In contrast to the innervation by the autonomic nervous system (ANS) via sympathetic and parasympathetic fibres in the normal heart, the transplanted heart is denervated because of the dissection of postganglionic neurons during OHT procedure (Kobashigawa & Olymbios, 2017). In spite of remaining innervated atria of recipients, there are no nerve impulses across the suture line (Kavanagh, 2005; Ramakrishna, Jaroszewski, & Arabia, 2009). Therefore, the chronotropic and inotropic responses of the transplanted heart must rely on circulating catecholamines from the adrenal glands (Nytrøen & Gullestad, 2013; Silva & Cipriano, 2016; Squires, 2011). However, intrinsic abilities of the donor heart, including electrical conduction and the Frank-Starling mechanism, are intact (Ramakrishna et al., 2009).

Due to the loss of parasympathetic control, i.e. the lack of vagal nerve innervation, donor sinus node activity is responsible for HR generation (Kavanagh, 2005; Ramakrishna et al., 2009). As a result, the resting HR is elevated by approximately 30% (Dennell, 2009) or 20bpm (Silva & Cipriano, 2016), or increased to approximately 95-115bpm (Squires, 2011). Due to the high resting HR, the resting stroke volume (SV) in HTRs decreases to maintain the resting cardiac output ($\dot{Q}$), relating to the Frank-Starling mechanism (Kavanagh et al., 1988).

In response to exercise, in the normal heart, sympathetic stimulation leads to rapid increased HR and then parasympathetic innervation lowers HR to resting levels (Awad et al., 2016). Due to the lack of neural control together with the elevated resting HR in HTRs, HR cannot draw an immediate response to exercise (Awad et al., 2016; Kavanagh, 2005). Firstly, according to an increase in $\dot{Q}$ via the Frank-Starling mechanism, the contraction of working muscles results in an increase in venous return, leading to increased left ventricular (LV) end-diastolic volume, resulting in increased SV (Kavanagh, 2005; Squires, 2011). Subsequently, a blunted increase in HR, driven by positive chronotropic action of catecholamines, contributes to an increase in $\dot{Q}$ after the first several minutes of exercise (Silva & Cipriano, 2016; Squires, 2011) despite insufficient increased myocardial contractility when compared with those from sympathetic control (Dennell, 2009). Peak HR during exercise is slightly lower than expected value, i.e. approximately 150 bpm (Silva & Cipriano, 2016; Squires, 2011) or 80% of normal value (Kavanagh, 2005), and this leads to a decrease in HR reserve in HTRs to 30-50 bpm (Kavanagh, 2005). Due to the lack of vagal activity, catecholamines also cause a delayed decrease in HR to the resting levels during recovery period

(Nytrøen & Gullestad, 2013). It takes 10-15 minutes to decrease plasma catecholamine levels after cessation of exercise (Dennell, 2009).

In terms of the systemic circulation in HTRs, afferent denervation interrupts the baroreflex control mechanisms (Silva & Cipriano, 2016). The loss of information to the hypothalamus and medulla oblongata results in an impairment of the renin-angiotensin-aldosterone system to respond to hypervolume (Dennell, 2009). As a result, blood volume is increased ≤14%, resulting from fluid retention (Dennell, 2009), and this may lead to a mild increase in the resting blood pressure in HTRs (Silva & Cipriano, 2016; Squires, 2011). However, systolic blood pressure (SBP) at peak exercise is decreased (Silva & Cipriano, 2016) to approximately 80% of normal value (Kavanagh, 2005). At peak exercise, the lower HR and SBP contribute to a 20% decrease in $\dot{Q}$ (Kavanagh, 2005).

Additionally, due to sensory afferent denervation, HTRs may not experience angina symptoms (Dennell, 2009), which are a warning sign for myocardial ischaemia (Ramzy et al., 2005) and this can prevent HTRs from early detection of CAV (Aranda & Hill, 2000).

II. Left ventricular dysfunction

It has been stated that although most HTRs have a preserved LVEF, an increase in LV filling pressure has been implicated in LV diastolic dysfunction (Squires, 2011), resulting in a below-normal SV at peak exercise (Silva & Cipriano, 2016; Squires, 2011). Despite indirect LV pressure measurements, Kao et al. (1994) found that the HTx group had the lower end-diastolic volume index by 14%, resulting in the lower SV index by 17% at peak exercise, when compared with the normal group. Due to these results,

Kao et al. (1994) also claimed that diastolic dysfunction might limit the ability to rely on the Frank-Starling mechanism to increase SV. Marconi and Marzorati (2003) stated that possible causes of diastolic dysfunction in HTRs may be a combination of a mismatch between the size of the donor heart and the body of recipients, a number of rejections, hypertension, and myocardial ischaemia, resulting from CAV.

III. Pulmonary function

Although lung volume, airway function and pulmonary haemodynamic abnormalities, caused by severe chronic HF, can be recovered to nearly normal in most HTRs, approximately 40% of HTRs (Squires, 2011) experience an impairment of alveolar gas diffusion, which may be due to pulmonary microvascular injury before surgery (Marconi & Marzorati, 2003). A below-normal increase in tidal volume during exercise may result from respiratory muscle weakness, hypoperfusion, deconditioning or the effect of long-term corticosteroid administration (Brubaker, Brozena, Morley, Walter, & Berry, 1997). In addition, ventilatory efficiency during exercise ($\dot{V}_E/\dot{V}_{CO_2}$slope) may be lower than normal (Squires, 2011). However, most HTRs still have normal value of arterial oxygen saturation at rest and during exercise (Squires, 2011).

IV. Muscle function and structure

Adverse effects on skeletal muscles from chronic HF during the pre-transplant period, including impaired vasodilation during exercise due to endothelial dysfunction, decreased fibre cross-sectional area, decreased capillary density, reduced content of mitochondria, decreased oxidative enzymes, increased anaerobic enzymes and conversion of slow-twitch muscle fibres towards fast twitch muscle fibres, remain apparent in HTRs (Braith & Edwards, 2000; Marconi & Marzorati, 2003; Squires, 2011).

Kao et al. (1994) found that, at rest and submaximal exercise, arteriovenous oxygen difference [(a-$\bar{v}$)O_2 diff] was normal in the HTx group; on the other hand, at maximal exercise, (a-$\bar{v}$)O_2 diff was decreased by 24%, when compared with the normal group. This may be caused by an impairment of oxidative capacity metabolism and peripheral oxygen delivery, relating to decreased capillary blood. Moreover, an above-normal increase in plasma lactate concentrations at peak exercise indicates metabolic insufficiency of skeletal muscle in HTRs (Braith & Edwards, 2000).

The use of corticosteroids, i.e. immunosuppressive agents (see Table 3), can lead to muscle wasting and decreased bone formation in HTRs. As for muscle atrophy, this is induced by corticosteroids by inhibiting the amino acid transport into muscles, resulting in protein synthesis limitation, and inhibiting myogenesis, leading to protein catabolism (Schakman, Gilson, & Thissen, 2008). Corticosteroids also result in osteoporosis by decreasing the rate of bone formation, the number of osteoblasts and osteocytes and their functions (Briot & Roux, 2015).

3.5 Major post-transplant complications

I. Allograft rejection

Allograft rejection can damage myocytes, leading to myocyte necrosis, which may result in LV dysfunction and HF (Squires, 2004). As regards immunosuppressant therapy (see section 3.3), graft rejection can result from underimmunosuppression; on the other hand, overimmunosuppression may cause infections to all organ allograft recipients (Hunt, 1998). A routine endomyocardial biopsy is required to detect rejection and is also useful to optimise intensity of immunosuppression (Dennell, 2009; Hunt, 1998; Squires, 2004). In the context of CR, the result of biopsy is also essential

for adjusting exercise programmes for HTRs (Dennell, 2009). Standardised acute rejection grading scale is outlined in Table 4 (Squires, 2004).

Table 4 Grading of acute rejection

Grade	**Level of rejection**
0	No rejection
1	Mild rejection
1A 1B	Focal infiltration without necrosis Diffuse but sparse infiltration, without necrosis
2	Moderate rejection One focus only with aggressive infiltration ± focal myocyte damage
3	Moderate rejection
3A 3B	Multifocal aggressive infiltration ± myocyte damage Diffuse inflammatory process with necrosis
4	Severe rejection Diffuse aggressive polymorphous infiltrates with necrosis

To prevent permanent damage to the myocardium, HTRs should be advised to not to exercise during severe rejection until the episode is resolved (Dennell, 2009). However, patients can continue exercise at current levels without progression during moderate rejection and slowly progress during an episode of mild rejection (Dennell, 2009).

II. Infection

A high level of immunosuppression is related to opportunistic infections in HTRs (Hunt, 1998). The major serious infection in HTRs is affected by cytomegalovirus (CMV) (Deng, 2002). Due to being the leading causes of death in the first year after transplantation (Lund et al., 2017), a therapeutic approach that focuses on infection management is useful for survival after HTx (Hunt, 1998). Moreover, to detect the first signs of an

infection, routine temperature monitoring is required (Association of Chartered Physiotherapists in Cardiac Rehabilitation [ACPICR], 2015).

III. Cardiac allograft vasculopathy

CAV, i.e. accelerated graft coronary disease (Squires, 2004), is a major long-term survival limitation of HTRs (Lund et al., 2017). Endothelial injury and fibroproliferative cellular responses, stimulated by vascular inflammation through either immunologic or nonimmunologic factors, leads to excessive tissue repair responses, resulting in circumferential intimal thickening (Chih, Chong, Mielniczuk, Bhatt, & Beanlands, 2016) and, eventually, blocking the coronary vessels, particularly the intramyocardial vessels (Ramzy et al., 2005). The immune response to the allograft is the factor that develops CAV in addition to immunosuppressant drugs, ischemia-reperfusion injury, CMV infection, and vascular risk factors, such as obesity, hypertension, hyperglycaemia and hyperlipidaemia (Chih et al., 2016; Squires, 2004).

Due to the limited treatment for CAV, re-transplantation is the only effective treatment option for severe CAV (Ramzy et al., 2005). Therefore, prevention of CAV through immune and nonimmune risk factors, such as optimising immunosuppressive therapy and lipid-lowering drugs together with lifestyle changes, is important for HTRs (Ramzy et al., 2005).

4. Exercise performance in heart transplant recipients

Chronotropic incompetence, i.e. an inadequate HR response to exercise (Brubaker & Kitzman, 2011), due to denervation, LV dysfunction, pulmonary limitations and abnormalities of skeletal muscle function and structure (see section 3.4) are associated with decreased $\dot{V}O_2$peak and exercise intolerance in HTRs (Braith & Edwards, 2000;

Marconi & Marzorati, 2003). These abnormal physiological responses are also cited in Nytrøen and Gullestad (2013) as possible factors that may be related to a decrease in exercise capacity in HTRs (see Table 5).

Table 5 Possible factors related to reduced exercise capacity in heart transplant recipients

Central factors	**Peripheral factors**
Reduced cardiac output	Reduced skeletal muscle function
Chronotropic incompetence	Reduced muscle mass
Reduced stroke volume	Reduced muscle strength
Systolic dysfunction	Reduced capillary density
Diastolic dysfunction	Reduced oxidative capacity
Pulmonary dysfunction	Reduced mitochondrial function
Pulmonary hypertension	Impaired vasodilatory capacity
Pulmonary congestion	Endothelial dysfunction
	Corticosteroid induced myopathy
	Deconditioning

A study of exercise capacity in well-trained HTRs (n =7), kidney transplant recipients (KTRs, n =6) and control subjects (CSs, n =6) showed that HTRs had the significantly lowest performance when compared with KTRs and CSs (maximal oxygen consumption [$\dot{V}O_2max$] [41.5±4.0, 52.0±8.7 and 50.6±9.0 ml/kg/min, respectively], maximal treadmill speed [9.9±1.2, 12.7±1.9 and 15.5±1.5 km/h, respectively] and HR reserve [65±17, 101±12 and 110±11 bpm, respectively], $P < .05$) (Richard et al., 2005). Additionally, a study of a CPX test in the early, i.e. after HTx <1 year, and the late HTR group, i.e. after HTx for 10 years, revealed that although the mean HR reserve of the early HTR group was lower than that of the late HTR group (39±15 vs. 58±19 bpm, respectively, $P = .049$) in addition to a decrease in HR recovery in the late HTR group (-

6.0±4.7% at the first minute and -15.5±2.4% at the second minute), there was no significant difference in $\dot{V}O_2$peak between the two groups (23.4±4 vs. 21.8±5 ml/kg/min, respectively, P = .56) and time of exercise testing (14±3 vs. 13±3 min, respectively, P = .95) (Carvalho et al., 2013). This means that despite an improvement in HR reserve and HR recovery, exercise capacity of HTRs cannot be restored over time. However, significant differences of recipients' characteristics, i.e. age (P = .003) and BMI (P = .049), should be taken into consideration and are clearly limitations of this study.

Furthermore, Nytrøen and Gullestad (2013) also state that co-morbidities, smoking, anxiety and depression and reduced HRQoL may limit exercise performance in HTRs.

5. Exercise-based cardiac rehabilitation for heart transplant recipients

Early mobilisation can be started as soon as HTRs are extubated after surgery (AACVPR, 2013; Dennell, 2009). Regarding inpatient ET, individuals may begin with exercise in bed, such as passive range-of-motion exercises for upper and lower extremities and active leg exercise, and can gradually progress to seated exercise, standing exercise and walking (AACVPR, 2013; Dennell, 2009). Exercise with machines, including cycle ergometry without adding resistance and treadmill walking at a slow pace, may be commenced, depending on an improvement of the individual's performance (AACVPR, 2013; Kavanagh, 2005) and episodes of rejection (see section 3.5) (AACVPR, 2013; Dennell, 2009).

As for exercise prescription for outpatients, while HR-based intensity is not appropriate for HTRs due to chronotropic incompetence, the use of rating of perceived exertion (RPE) scale is recommended, i.e. 11-14 on the Borg RPE scale (AACVPR, 2013;

ACPICR, 2015; ACSM, 2018). It is important to note that due to the delayed HR responses, caused by catecholamines, HTRs need a longer time to warm-up and cool-down, i.e. 10-15 minutes each (ACPICR, 2015).

ET for HTRs should include not only aerobic exercise, but also resistance training to counteract the adverse side effects of immunosuppressant therapy on bone and skeletal muscle (see section 3.4) (AACVPR, 2013; ACSM, 2018). Braith et al. (2003) reported that despite there being a significant lower ($P \leq .05$) total body bone mineral density (BMD) of HTRs, who received cyclosporine, prednisone and azathioprine, at 2-month post-HTx (-2.7±1.0%) when compared with pre-HTx values, no significant difference values (-0.9±0.2%) were found in HTRs who participated in 6-month resistance training and received alendronate. Although no subjects participated in resistance training alone, this study may indicate that adding resistance ET to an anti-osteoporosis regimen can reverse steroid-induced bone loss in HTRs.

Kobashigawa et al. (1999) compared the effects of ET in 14 HTRs (the exercise group), who participated in exercise rehabilitation programmes (i.e. strengthening, flexibility and moderate-intensity aerobic exercises), with 13 HTRs (the control group), who participated in non-formal exercise sessions with written exercise guidelines between 1- and 6-month post-transplant. The exercise group showed superior outcomes (mean difference), when compared with the control group, in $\dot{V}O_2$peak (4.4 vs. 1.9 ml/kg/min, respectively, $P = .01$), the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$) (-13 vs. -6, respectively, $P = .02$) and the sit-to-stand rate within 1 minute (i.e. the modified muscle strength testing) (13.3 vs. 5.6 no./min, respectively, $P = .02$) (Kobashigawa et al., 1999). This study revealed that HTRs who received individualised exercise

programmes had an increase in exercise capacity and muscle performance, which can indicate improved QOL (Kobashigawa et al., 1999), in spite of the lack of the non-exercise group.

Comparison between HTRs with regular exercise (the training group; 7 men) and non-exercise (the non-training group; 6 men) and healthy participants (the control group; 6 men) were carried out by Schmidt et al. (2002). While the training group participated in ET programme with 2-3 day/week of stationary cycling for ≥6 months, a sedentary lifestyle with exercise ≤1 day/week was defined as the non-training group (Schmidt et al., 2002). A regular aerobic exercise not only increased $\dot{V}O_2$peak significantly (P = .05) by 16±8% in the training group, but it also improved vascular function by increasing flow-mediated vasodilation (percentage difference: 8.4±2.2% vs. 7.1±2.4% vs. 1.4±0.8% for the control, training and non-training groups, respectively, P < .05) (Schmidt et al., 2002). This means that aerobic exercise may improve endothelial function (EnF) in HTRs, although it remains inferior to age-matched healthy individuals. However, the small size of each group and the only male participants in this study limited the strength of the results.

A study that included 43 HTRs showed that supervised aerobic and strength training for 12 weeks resulted in the greater increase in $\dot{V}O_2$peak by 3.11 ml/kg/min (95% CI 1.2-5.0, P = .003), chest-press and leg-press strength by 10.4 kg (5.2-15.5) and 34.7 kg (3.7-65.6), respectively, and leg and total lean tissue mass (LTM) by 0.78 kg (0.31-1.3) and 1.34 kg (0.34-2.3), respectively, in training HTRs, compared with no-training HTRs (Haykowsky, Taylor, Kim, & Tymchak, 2009). However, no improved LV systolic function and brachial artery EnF in this study indicated that increased exercise capacity

of HTRs may predominantly rely on peripheral skeletal muscle adaptations through oxygen utilization improvement (Haykowsky et al., 2009).

Decreased resting HR (MD -5 [95% CI (-9)-0], P = .04), increased peak HR (5 [0-10], P = .035) and increased HR reserve (10 [4-16], P = .002) were found in HTRs after performing HIIT (Nytrøen et al., 2012). This means that ET may alleviate chronotropic incompetence in HTRs.

Due to effects of exercise on reduced arterial wall thickness (Thijssen, Cable, & Green, 2012) and vascular risk factors, including obesity and plasma lipids (Swift et al., 2013), which are possible factors to develop CAV (see section 3.5), exercise-based CR in HTRs may reduce the progression of CAV. Thottam et al. (2013) found that CR was related to decreased 5-years progression of CAV in HTRs when compared with HTRs without CR (85% vs. 76%, respectively, P = .024) despite a significant difference of recipient age (54±12 vs. 58±11, respectively, P = .001). Additionally, by using intravascular ultrasonography, Nytrøen et al. (2013) revealed that HTRs participated in HIIT had a smaller rate of CAV progression when compared with control participants. The mean increase in percent atheroma volume (0.9% [95% CI (-0.3)-1.9], total atheroma volume (0.3 mm^3/mm [0.0-0.6] and maximal intimal thickness (0.02 mm [(-0.01)-0.04] in the HIIT group was lower than that of the control group (P = .021, .020 and .054 [marginal significance], respectively) (Nytrøen et al., 2013).

However, regarding studies of HIIT by Nytrøen et al. (2012) and Nytrøen et al. (2013). HTRs who participated in standard programmes were defined as control participants. In this way, non-exercise participants are needed to determine whether usual exercise

or HIIT results in reversal of chronotropic incompetence and reduce the progression of CAV in HTRs, respectively.

The latest Cochrane review of exercise-based CR in HTRs (Anderson et al., 2017) reported the greater $\dot{V}O_2$peak improvement by 2.49 m/kg/min (95% CI 1.63-3.36) for patients participating in ET programme versus non-exercise HTRs and 2.30 ml/kg/min (0.59-4.01, P < .001) for those who undertook HIIT versus continued moderate-intensity training (CMIT). As for HRQoL, an improvement from ET cannot be concluded due to the variation in methods and outcomes of each study. Also, in terms of HIIT versus CMIT, there were no statistically significant differences between groups (Anderson et al., 2017). Due to the short periods of follow up, i.e. a median of 12 months, this may not be adequate duration for detecting any changes from HTRs.

There are very limited studies which have performed the long-term of ET after HTx. Despite the small sample size, Kavanagh et al. (2003) have successfully investigated a study of 12-year follow-up in 20 surviving HTRs who received the 16-month ET programme and were advised to continue exercise from their final prescription, compared with the age-matched healthy controls. In spite of an increase in $\dot{V}O_2$peak from 22.2±4 to 27.9±7 ml/kg/min in HTx survivors at 16 months, $\dot{V}O_2$peak decreased to 23.7±6 ml/kg/min at 12 years, accounting for 0.39 ml/kg/min/year (Kavanagh et al., 2003). Due to the similar rate of decline in the controls group, i.e. 0.37 ml/kg/min/year, this may be caused by the normal ageing process (Kavanagh et al., 2003). Moreover, although lean body mass of HTRs increased from 56.7±5 to 62.3±8 kg at 12 years, it was lower than the controls (65.7±7 kg); therefore, resistance training is needed (Kavanagh et al., 2003).

6. Conclusion

Although survival after HTx has increased over time, unique physiological changes due to cardiac ANS denervation, immunosuppressant therapy and prolonged de-conditioning from chronic HF result in abnormalities, such as chronotropic incompetence and peripheral muscle dysfunction, leading to exercise intolerance in HTRs. ET not only improves $\dot{V}O_2$peak and chronotropic responses to exercise in HTRs, but it also counteracts the adverse side effects of immunosuppressive agents on skeletal muscle performance. The provision of exercise-based CR, which consists of aerobic, resistance and flexibility exercise, is advantageous for HRTs by improving exercise capacity in addition to reduced progression of CAV through HIIT. However, the fact that the normal ageing process may affect long-term outcomes in HTRs needs to be taken into consideration.

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Research study:

A systematic review

1. The appropriate journal for publishing a study

The aim of this review was to examine effectiveness of exercise interventions in patients post cardiac transplantation, hence it is appropriate for publication in a medical, health science or education journal, covering articles on aspects of heart transplantation. The Journal of Heart and Lung Transplantation covers research in the field of cardiac and pulmonary transplantation. The scope of its content is not only limited to surgery but covers allied health sciences in the field of cardiopulmonary transplantation, including exercise intervention, physiotherapy and cardiac rehabilitation. Several articles cited in the review were found in this journal during database searching, which highlights its eminence and impact in the field.

2. Abstract

Objectives

The aim of this systematic review is to determine the effects and safety of exercise-based cardiac rehabilitation (CR) on exercise capacity in elderly patients who undergo heart transplantation (HTx).

Methods

Relevant studies of exercise-based CR in heart transplant recipients (HTRs) aged ≥55 years were systematically searched through PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Web of Science. The Physiotherapy Evidence Database (PEDro) scale was used to determine study quality.

Results

Five studies, which included four randomised controlled trials (RCTs) and one uncontrolled trial (UCT), met the inclusion criteria for the review. The selected studies had participants with a median age of 57 years (range 55-60.6 years). The exercise programmes conducted in the studies had a training duration ranging from 8-48 weeks. Aerobic and strength training were used in all studies. After the training periods, a significant increase in peak oxygen consumption ($\dot{V}O_2$peak) was reported in the majority of studies. Three RCTs reported improved lower extremity muscular strength. When compared with controls, increased peak heart rate (HR) in training participants was found in only one RCT with a 1-year programme of high-intensity interval training (HIIT). All studies did not show any significant changes in cardiovascular function and no adverse events were reported.

Conclusion

Exercise-based CR is safe and can improve exercise capacity in elderly HTRs who are clinically stable through an improvement in peripheral muscular performance. A ≥1-year HIIT programme is likely to be more effective than usual exercise by improving peak HR in elderly HTRs.

Keywords: heart transplant, elderly, exercise training, exercise capacity

3. Introduction

Although people living with and dying from heart failure (HF) are increasing, there have been effective treatments that can improve quality of life (QOL) and survival of these patients (Ponikowski et al., 2014). As for end-stage HF, HTx is the gold standard treatment (Yancy et al., 2013). The comparison of one-, three- and five-year survival rates of adult HTRs in the United States between the 2013 Annual Data Report (88.1%, 81.3% and 75.3%, respectively) (Colvin-Adams et al., 2015) and the 2016 report (90.1%, 83.5% and 78.3%, respectively) (Colvin et al.,2018) indicates that the survival rates of adult HTRs have improved. Also, the incidence of allograft rejection after transplant has decreased due to an improvement of immunosuppressive modalities (Lund et al., 2017). HTx not only reduces mortality of HF patients with high risk of dying (Deng, De Meester, Smits, Heinecke, & Scheld, 2000), but also improves overall QOL compared with patients on the waiting list (Mantovani et al., 2016).

Between 1982-1998 and 2009-6/2016 periods, data from the Registry of the International Society for Heart and Lung Transplantation (ISHLT) revealed that although patients aged 40-59 years were a large number of HTRs, this proportion declined from 59.82% to 43.86% for each period, respectively; on the other hand, a growth from 16.37% to 26.19% of 60-69 years of age and from 0.27% to 1.82% of ≥70 years of age for each period, respectively, indicated that older recipients increased gradually (Lund et al., 2017). Despite the extended upper age limit for HTx candidates to 70 years old (Mehra et al., 2006), the outcomes of HTx in elderly patients are controversial. Elderly HTRs have been reported to have poorer survival (Cooper et al., 2016; Lund et al., 2017; Samsky et al., 2013; Sponga et al., 2016; Tjang, van der

Heijden, Tenderich, Körfer, & Grobbee, 2008) in addition to higher infection rate and increased hospital stay (Weiss, Nwakanma, Patel, & Yuh, 2008), and higher incidence of rejection (Jamil et al., 2017) compared to that of younger counterparts. By contrast, it has been argued that elderly HTRs have fewer rejection episodes (Baron et al., 1999; Bull et al., 1996; Demers et al., 2003; Weiss et al., 2008; Zuckermann et al., 2003) as well as equivalent morbidity and mortality (Baron et al., 1999; Blanche et al., 1996; Blanche et al., 2001; Demers et al., 2003; Jamil et al., 2017; Zuckermann et al., 2003) compared with those in younger counterparts.

The denervated transplanted heart leads to unique characteristics, such as chronotropic incompetence, left ventricular (LV) dysfunction, and abnormal skeletal muscle function and structure, resulting in decreased exercise capacity in HTRs (Braith & Edwards, 2000; Marconi & Marzorati, 2003; Nytrøen & Gullestad, 2013). Exercise capacity has been claimed a strong predictor of the risk of death in both healthy individuals and patients with cardiovascular disease (CVD) (Myers et al., 2002). Therefore, improving exercise capacity is important to reduce mortality for HTRs.

In 1999, Kobashigawa et al. stated that improved exercise capacity and QOL in HTRs may result from the early introduction of exercise training (ET) after HTx. Moreover, a 2017 Cochrane review showed that exercise-based CR can improve exercise capacity in HTRs, who had a median age of 54.4 years (range 45-60.6 years) (Anderson et al., 2017). Although the advantage of exercise-based CR in HTRs on increased exercise capacity has been documented in the latest Cochrane review, there is less focus on HTRs of advanced age, which are increasing over time; this group deserves further

attention. Therefore, the purpose of this current systematic review is to determine the effects and safety of exercise-based CR on exercise capacity in elderly HTRs.

4. Methods

Due to being a dissertation of Master's degree, this systematic review has been conducted by a single reviewer.

4.1 Search strategy

Three databases, namely PubMed, CINAHL and Web of Science, were used to search for articles regarding HTx, exercise-based CR and exercise capacity. Search terms included cardiac or heart transplantation, cardiac rehabilitation, exercise training, exercise programme, physiotherapy, exercise capacity, exercise performance and oxygen consumption (see Appendix A). To avoid leaving out any relevant published articles, no filters were applied for age ranges of study population, study design, publication year or language. The search strategy was completed in July 2018.

4.2 Selection criteria

As for inclusion criteria, studies of exercise-based CR in HTRs were included. Exercise-based interventions could be ET alone or ET in addition to other components of comprehensive CR programme, such as health education and psychosocial health components. Furthermore, ET could be a supervised or unsupervised structured programme as well as a centre- or home-based programme for inpatients or outpatients. If the control group was included, participants in this group must not have received structured exercise above their normal pre-study routine but may have received standard medical care, non-exercise interventions of comprehensive CR, unstructured exercises or general advice on physical activity.

Regarding types of participants, older HTRs were adopted. Advanced age in HTx have been reported as ≥55 years (Borkon et al., 1999; Tjang et al., 2008), ≥60 years (Baron et al., 1999; Bull et al., 1996; Demers et al., 2003; Weiss et al., 2008; Zuckermann et al., 2003), ≥65 years (Blanche et al., 1996; Jamil et al., 2017; Samsky et al., 2013) and ≥70 years (Blanche et al., 2001). Due to the lack of a clear definition of elderly HTRs, studies that had the average age of participants ≥55 years were selected in this systematic review to maximise outcome data.

In terms of exclusion, studies were excluded on the following criteria: no full-text available, not published in English and the average age of participants <55 years, particularly the training group. Moreover, studies that included control participants who received ET above their normal pre-study routine were also excluded.

4.3 Selection of studies

Firstly, after removing duplicate articles, titles and abstracts, resulting from the search strategy, were initially screened on the basis of the inclusion criteria. Then, the full text of the remaining articles was assessed for eligibility with the full selection criteria. Finally, the articles that met the full eligibility criteria were included for data extraction.

4.4 Data extraction

Extracted data included study design, the country, source of funding, objectives, study setting (location), total duration of study, number of participants, number of drop outs, participants' mean age, time since HTx, component of the intervention, content of the exercise intervention (mode or type of exercise, intensity, frequency, and time per session), exercise testing method, outcomes on exercise capacity and all relevant

outcomes to exercise (e.g. muscle performance), adverse events, results with statistical significance, key points of discussion and conclusions.

4.5 Assessment of study validity

Study validity were assessed by using the PEDro scale, which consists of 11 items, including stated eligibility criteria, the use of random and concealed allocation procedure, baseline comparability, blinding of all subjects, therapists and assessors, adequate follow-up, the use of intention-to-treat analysis, reporting the results of between-group statistical comparisons, and providing both point estimates and variability (see Appendix B) (PEDro, 1999). A total score out of 10 comes from each satisfied item, except for item 1, which relates to external validity (PEDro, 1999).

5. Results

The results of the search through databases were 1972 articles. After removing 861 duplicates, another 1088 articles were excluded based on titles and abstracts. The remining 23 articles were retrieved to assess the full-text documents. Then, 18 articles were removed due to participant age (n = 12), non-full-text articles (n = 5) and non-English article (n = 1) (see Appendix C). Finally, a total of five studies met the inclusion criteria and were included in this systematic review. As for the validity of included studies, the PEDro scores ranged from 3/10 to 7/10 (see Appendix D). Summary of the study selection process is shown in Figure 1. Also, details of included studies are listed in Appendix E.

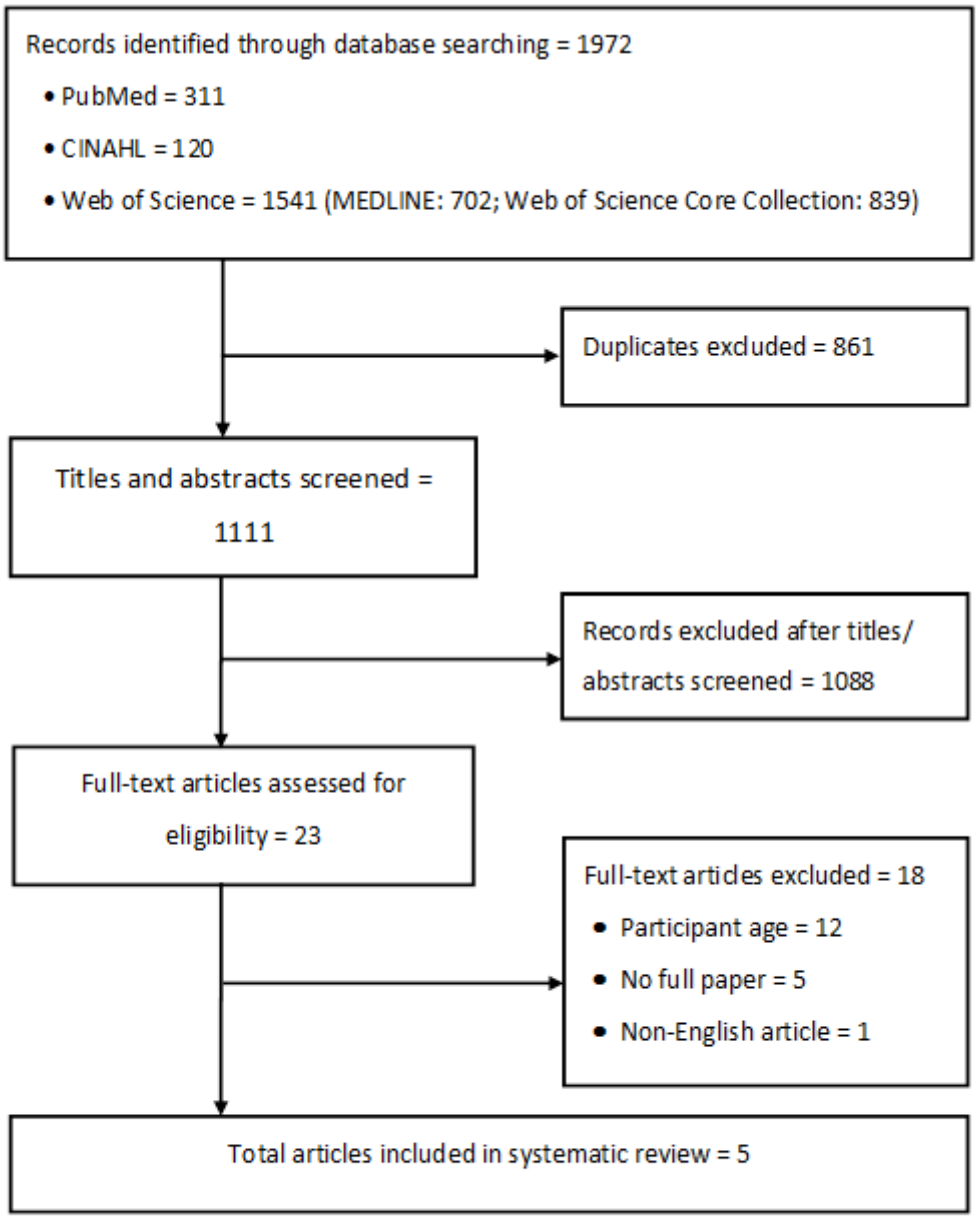

Figure 1 Study selection flow chart

Table 6 Characteristics of the included studies on study groups

Study	Study design	Number of participants	Age of participants	Time since HTx	Setting	Intervention	Duration
Haykowsky, Taylor, Kim, & Tymchak (2009)	RCT	Training n = 22 Drop out (% of drop out within group) n = 1 (4.5%)	Training (mean ± SD): 57 ± 10 years	Training (mean ± SD): 5.4 ± 4.9 years	Centre	Training: - Aerobic and strengthening exercises	12 weeks
		Control n = 21 Drop out (% of drop out within group) n = 2 (9.5%)	Control (mean ± SD): 59 ± 11 years	Control (mean ± SD): 4.4 ± 3.3 years		Control: - No training and exercise guidelines - Continue usual activities of daily living	
Kobashigawa et al. (1999)	RCT	Training n = 14 Drop out (% of drop out within group) n = NS	Training (mean ± SD): 55 ± 8 years	Control: 0.04 years	Centre	Training: - Aerobic, strengthening and flexibility exercises - Written home exercise guidelines	24 weeks
		Control n = 13 Drop out (% of drop out within group) n = NS	Training (mean ± SD): 50 ± 12 years	Control: 0.04 years		Control: - No formal, supervised exercise sessions - Written home exercise guidelines	
Rustad, Nytrøen, Amundsen, Gullestad, & Aakhus (2014)	RCT	Training n = 26 Drop out (% of drop out within group) n = 2 (7.7%)	Training (median [range]): 56 (20-72) years	Training (median [range]): 5 (1-8) years	Centre	Training: - Aerobic exercise (HIIT)	48 weeks
		Control n = 26 Drop out (% of drop out within group) n = 2 (7.7%)	Control (median [range]): 58 (19-71) years	Control (median [range]): 4 (1-7) years		Control: - Requested to continue routine exercise	
Wu et al. (2008)	RCT	Training n = 14 Drop out (% of drop out within group) n = 2 (14.3%)	Training (mean ± SD): 60.6 ± 6.2 years	Training (mean ± SD): 1.6 ± 1.8 years	Home	Training: - Aerobic and strengthening exercises	8 weeks
		Control n = 23 Drop out (% of drop out within group) n = 4 (17.4%)	Control (mean ± SD): 51.6 ± 12.8 years	Control (mean ± SD): 2.6 ± 1.9 years		Control: - No training - Keep usual activity lifestyle	
Haykowsky et al. (2005)	UCT	Training n = 18 Drop out (% of drop out within group) n = 1 (4.5%)	Training (mean ± SD): 57 ± 6 years	Control: 0.08 years	Centre	Training: - Aerobic and strengthening exercises	12 weeks
		No control group	No control group	No control group		No control group	

HIIT, high-intensity interval training; HTx, heart transplantation; NS, not stated; RCT, randomised controlled trial; UCT, uncontrolled trial

5.1 Study design and population

Table 6 shows description of the study design and participants of the five included studies, which consisted of four RCTs (Haykowsky, Taylor, Kim, & Tymchak, 2009; Kobashigawa et al., 1999; Rustad, Nytrøen, Amundsen, Gullestad, & Aakhus, 2014; Wu et al., 2008), and one UCT (Haykowsky et al., 2005).

The training duration ranged from 8 weeks to 48 weeks (1 year). Most studies used a centre-based exercise programme for the training group, while one study used home-based exercises (Wu et al., 2008). However, participants in Kobashigawa et al. (1999) received written exercise guidelines to exercise at home.

A median age of participants participated in the exercise programmes was 57 years (range 55-60.6 years) with a median time since HTx of 1.6 years (range 0.04-5.4). Drop-out participants were reported in three studies (Haykowsky et al., 2009; Rustad et al., 2014; Wu et al., 2008). The percentage of drop outs ranged from 4.5% to 14.3% for the training group and ranged from 9.5% to 17.4% for the control group.

Table 7 Summary of exercise interventions of the included studies

Study	Type of exercise	Training method/ equipment	Frequency	Intensity	Time per session
Haykowsky, Taylor, Kim, & Tymchak (2009)	Aerobic	Treadmill and cycle	- First 8 weeks: 5 days/week - Final 4 weeks: 3 days/week for CT; 2 days/week for IT	- First 8 weeks: 60-80% $\dot{V}_{O_2}$peak - Final 4 weeks: 80% $\dot{V}_{O_2}$peak for CT; 90-100% baseline PO (cycle) for IT	- First 8 weeks: 30-45 minutes - Final 4 weeks: 45 minutes for CT; 15-37.5 minutes for IT
	Strength	Upper and lower extremity strength training	2 days/week	50% of maximal strength	1-2 sets of 10-15 repetitions
Kobashigawa et al. (1999)	Aerobic	Treadmill, bicycle or arm ergometer	- For centre-based: initially, 1-3 times/week and gradually reduced to 1 time/ 2 weeks	Moderate intensity (due to patient's tolerance)	≥ 30 minutes (for CT)
	Strength	Closed-chain resistive and abdominal exercises		NS	NS
	Flexibility	Chest expansion and thoracic mobility exercises		NS	NS
Rustad, Nytrøen, Amundsen, Gullestad, & Aakhus (2014)	Aerobic	Treadmill (walking or running uphill)	3 sessions/week	- Intervals: 85-95% of peak HR - Active pauses: RPE 11–13	≥ 38 minutes (10-minute warm-up; 4 x 4-minute intervals with 3-minute active pause; NS cool-down)

CT, continuous training; HR, heart rate; IT, interval training; NS, not stated; PO, power output; RPE, rating of perceived exertion; $\dot{V}_{O_2}$peak, peak oxygen consumption

Table 7 Summary of exercise interventions of the included studies (continued)

Study	Type of exercise	Training method/ equipment	Frequency	Intensity	Time per session
Wu et al. (2008)	Aerobic	Walking and stepping exercises	≥ 3 times/week	For walking: RPE 12-14 (equivalent to 60-70% $\dot{V}_{O_2}$peak)	≥ 35 minutes (5-minute warm-up; NS time of strength training; walking 15-20 minutes and stepping 10 minutes; 5-minute cool-down)
	Strength	Upper and lower extremity strength training		NS	
Haykowsky et al. (2005)	Aerobic	Treadmill and/or bicycle	5 days/week	RPE 12-14	30-40 minutes
	Strength	Lower extremity resistance training	NS	50% of maximal strength, progressively increased as tolerated	3-5 sets of 10 repetitions

CT, continuous training; HR, heart rate; IT, interval training; NS, not stated; PO, power output; RPE, rating of perceived exertion; $\dot{V}_{O_2}$peak, Peak oxygen consumption

5.2 Exercise training

Description of exercise interventions of the included studies is outlined in Table 7. All studies used aerobic and strength training. Also, one study added flexibility exercise into the training programme (Kobashigawa et al., 1999).

As for the aerobic exercise, treadmill walking and static cycling were most commonly used. The reported training intensity ranged widely across studies. Moderate intensity was set for continuous training (CT) by using a percentage of $\dot{V}O_2$peak, which was 60-80% $\dot{V}O_2$peak (Haykowsky et al., 2009), and the Borg's rating of perceived exertion (RPE) 6-20 scale, which was RPE 12-14 (Haykowsky et al., 2005; Wu et al., 2008), as well as individualised intensity (Kobashigawa et al., 1999). The use of HIIT was also reported in two trials, which based intensity during the work periods on 85-95% of peak HR for walking or running uphill on a treadmill (Rustad et al.,2014) and 90-100% of baseline power output (PO) for cycling (Haykowsky et al., 2009). The frequency and session length ranged from 3 to 5 days/week and from 30 to 45 minutes, respectively.

Strengthening exercises for upper (e.g. chest press and arm curls) and lower (e.g. leg press, bridging and half-squats) extremities were most commonly used. Abdominal exercise was also included in one study (Kobashigawa et al., 1999). Two studies reported that strength training was performed in the same training sessions with aerobic exercise but did not state session length and intensity (Kobashigawa et al., 1999; Wu et al., 2008). Two studies reported dose of training with intensity of 50% of maximal strength, 1-5 sets with 10-15 repetitions (Haykowsky et al., 2005; Haykowsky et al., 2009). However, only the study of Haykowsky et al. (2009) reported the strength training frequency of 2 days/week.

5.3 Results of exercise capacity testing

According to Table 8, a maximal exercise test was used to assess exercise capacity. A bicycle ergometer was most commonly conducted, while a treadmill was only used in one study (Rustad et al., 2014). $\dot{V}O_2$peak and peak HR were reported as exercise capacity outcomes in the majority of trials. Peak workload, peak PO, peak respiratory exchange ratio (RER), resting HR, resting systolic blood pressure (SBP), peak SBP and minute ventilation ($\dot{V}E$) were also the most commonly reported outcomes.

Regarding the comparison of each variable between baseline and after interventions of the training participants (see Table 8). All studies showed a positive effect on exercise capacity. The majority of studies reported an increase in both $\dot{V}O_2$peak and peak HR after the training period. Two studies reported a significant increase in $\dot{V}O_2$peak and peak HR (Haykowsky et al., 2005; Rustad et al., 2014). One study also reported an increase in both $\dot{V}O_2$peak and peak HR by the percentage change (Kobashigawa et al., 1999). The mean increase in $\dot{V}O_2$peak and peak HR ranged from +3.2 to +6.0 ml/kg/min and from +4 to +25 bpm, respectively. Moreover, a significant increase in peak PO was reported by Haykowsky et al. (2005). Also, increased peak workload, peak SBP and $\dot{V}E$ were reported due to increased change after interventions. As for resting HR and resting SBP, there were conflicting data between two trials (Kobashigawa et al., 1999; Wu et al., 2008).

Table 8 Summary results of exercise capacity testing: Comparison between baseline and post-interventions of the training subjects

Study	Test method/ equipment	Parameter	Baseline	Post-training	Mean change
Haykowsky, Taylor, Kim, & Tymchak (2009)	Maximal exercise test/ bicycle ergometer	$\dot{V}_{O_2}$peak (ml/kg/min)	21.2 ± 7.3	24.7 ± 8.8	+3.43[NS]
		Peak HR (bpm)	147 ± 18	154 ± 15	+7[NS]
		Peak PO (W)	108 ± 36	131 ± 45	+23[NS]
		Peak RER	1.11 ± 0.10	1.15 ± 0.07	+0.04[NS]
		Peak SBP (mmHg)	175 ± 26	177 ± 21	+2[NS]
Kobashigawa et al. (1999)	Maximal exercise test/ bicycle ergometer	$\dot{V}_{O_2}$peak (ml/kg/min)	9.2	13.6	+4.4[NS] (+49%)[PC]
		Peak HR (bpm)	102	125	+23[NS] (+23%)[PC]
		Peak workload (W)	59	94	+35[NS] (+59%)[PC]
		Resting HR (bpm)	90	100	+10[NS] (+11%)[PC]
		Resting SBP (mmHg)	126	121	-5[NS] (-4%)[PC]
		Peak SBP (mmHg)	141	148	+7[NS] (+5%)[PC]
		$\dot{V}_E$ (l/min)	38	45	+7[NS] (+18%)[PC]
Rustad, Nytrøen, Amundsen, Gullestad, & Aakhus (2014)	Maximal exercise test/ treadmill	$\dot{V}_{O_2}$peak (ml/kg/min)	27.7 ± 5.5	30.9 ± 5.3	+3.2[*]
		Peak HR (bpm)	159 ± 14	163 ± 13	+4[**]
		Peak RER	1.07 ± 0.06	1.08 ± 0.04	+0.01[***]
Wu et al. (2008)	Maximal exercise test/ bicycle ergometer	$\dot{V}_{O_2}$peak (ml/kg/min)	12.1 ± 2.7	13.2 ± 3.9	+1.0[NS]
		Peak HR (bpm)	120.6 ± 15.8	121.6 ± 16.7	+1.1[NS]
		Peak workload (W)	55.1 ± 17.3	64.9 ± 19.3	+9.7[NS]
		Resting HR (bpm)	96.3 ± 8.7	95.2 ± 6.8	-1.1[NS]
		Resting SBP (mmHg)	129.3 ± 16.4	130.6 ± 14.9	+1.3[NS]
		$\dot{V}_E$ (l/min)	41.9 ± 9.5	44.6 ± 10.6	+2.7[NS]
Haykowsky et al. (2005)	Maximal exercise test/ bicycle ergometer	$\dot{V}_{O_2}$peak (ml/kg/min)	14	20	+6[**]
		Peak HR (bpm)	109 ± 14	134 ± 15	+25[**]
		Peak PO (W)	79 ± 21	113 ± 31	+34[**]

Values are reported as mean/ mean ± SD; [NS] not stated P value; [PC] percentage change; [*] P ≤ .001; [**] P < .05; [***] P > .05. HR, heart rate; PO, power output; RER, respiratory exchange ratio; SBP, systolic blood pressure; $\dot{V}_E$, minute ventilation

As for the comparison between the training and the control groups (see Table 9), most RCTs reported a significantly higher $\dot{V}O_2$peak in the training group. The mean increase ranged from +2.5 to +3.7 ml/kg/min. However, one study reported no significant changes of $\dot{V}O_2$peak between both groups (Wu et al., 2008). Two RCTs reported that peak workload was significantly higher in the training group, accounting for +23 W in Kobashigawa et al. (1999) and +10.7 W in Wu et al. (2008) compared to the controls. Additionally, one study reported significantly higher peak PO (+20.9 W) in the training group (Haykowsky et al., 2009).

Regarding the change of peak HR in RCTs, the significantly greater value in the training group was reported in one study (Rustad et al., 2014), while the other three RCTs reported no significant changes compared to the controls.

Furthermore, for the other variables, including peak RER, resting HR, SBP, $\dot{V}E$, no significant differences were reported between the training and control groups.

Table 9 Summary results of exercise test: Comparison between the training and control groups in the included randomised controlled trials

Study	Parameter	Control			Training	Difference between group
		Baseline	Post-training	Mean change	Mean change	
Haykowsky, Taylor, Kim, & Tymchak (2009)[$]	$\dot{V}_{O_2}$peak (ml/kg/min)	18.2 ± 5.9	18.2 ± 5.3	0.04	+3.43	3.11**
	Peak HR (bpm)	139.1 ± 19	139.0 ± 20	-0.05	+7.0	6.73***
	Peak PO (W)	106 ± 27	107 ± 30	+0.8	+23	20.9*
	Peak RER	1.09 ± 0.08	1.10 ± 0.1	+0.01	+0.04	0.04***
	Peak SBP (mmHg)	172 ± 29	180 ± 27	+8	+2	9.5***
Kobashigawa et al. (1999)	$\dot{V}_{O_2}$peak (ml/kg/min)	10.4	12.3	+1.9	+4.4	2.5**
	Peak HR (bpm)	107	134	+27	+23	4***
	Peak workload (W)	66	78	+12	+35	23**
	Resting HR (bpm)	91	109	+18	+10	8***
	Resting SBP (mmHg)	130	114	-16	-5	11***
	Peak SBP (mmHg)	139	148	+9	+7	2***
	$\dot{V}_E$ (l/min)	46	62	+16	+7	9***
Rustad, Nytrøen, Amundsen, Gullestad, & Aakhus (2014)	$\dot{V}_{O_2}$peak (ml/kg/min)	28.5 ± 7.0	28.0 ± 6.7	-0.5	+3.2	3.7*
	Peak HR (bpm)	154 ± 15	154 ± 17	0	+4	4**
	Peak RER	1.06 ± 0.05	1.07 ± 0.05	+0.01	+0.01	0***
Wu et al. (2008)	$\dot{V}_{O_2}$peak (ml/kg/min)	13.7 ± 3.3	13.2 ± 3.7	-0.5	+1.0	1.6***
	Peak HR (bpm)	132.7 ± 15.7	130.8 ± 14.1	-2.0	+1.1	3.1***
	Peak workload (W)	73.5 ± 23.4	72.6 ± 20.9	-1.0	+9.7	10.7**
	Resting HR (bpm)	97.0 ± 7.0	96.0 ± 6.7	-1.1	-1.1	0***
	Resting SBP (mmHg)	121.9 ± 14.6	122.1 ± 13.0	+0.2	+1.3	1.1***
	$\dot{V}_E$ (l/min)	45.4 ± 10.9	45.2 ± 10.9	+0.3	+2.7	2.4***

Values are reported as mean/ mean ± SD; [$] difference values between groups after adjusted analysis; * P < .001; ** P < .05; *** P > .05. HR, heart rate; PO, power output; RER, respiratory exchange ratio; SBP, systolic blood pressure; $\dot{V}_E$, minute ventilation

5.4 Effects on muscle performance

According to Table 10, three RCTs showed that the improvement of lower extremity muscular strength in the training group was significantly greater than that in the control group for the sit-to-stand rate in 1 minute (Kobashigawa et al., 1999; Wu et al., 2008) and leg-press strength (Haykowsky et al., 2009). Although Wu et al. (2008) reported a significant improvement in muscle fatigue index, there was no significant difference in isometric maximal strength of quadriceps using an isokinetic dynamometer. One trial reported that chest-press strength was significantly higher in the training group when compared with the controls but no significant improvements in other muscle groups of the upper limbs were reported (Haykowsky et al., 2009). Additionally, a significant effect of ET on increased leg and total lean tissue mass (LTM) was also reported in the study of Haykowsky et al. (2009).

5.5 Effects on cardiovascular function

In Table 10, submaximal cycle exercise echocardiographic test was conducted to assess cardiovascular function of HTRs in both UCT and RCTs (Haykowsky et al., 2005; Haykowsky et al., 2009; Rustad et al., 2014). These studies did not show any significant improvement in cardiovascular function, including LV systolic function, stroke volume (SV) and cardiac output [$\dot{Q}$], in HTRs after the training period. Moreover, one study reported that there were no significantly changes in brachial artery endothelial function (EnF) in the training group compared with controls (Haykowsky et al., 2009).

5.6 Adverse events

No adverse events related to ET were reported in the included studies (see Table 10).

Table 10 Summary of outcomes regarding muscle performance, cardiovascular function and adverse event

Study	**Test method**	**Outcome**
1. **Muscle performance**		
Haykowsky, Taylor, Kim, & Tymchak (2009)[RCT]	1-RM test	↑ Leg-press (34.7 kg, 95% CI 3.7-65.6)[*] ↑ Chest-press (10.4 kg, 95% CI 5.2-15.5)[*] ↔ Latissimus dorsi pulldown and arm curl[**]
	Dual energy x-ray absorptiometry	↑ Leg LTM (0.78 kg, 95% CI 0.31-1.3)[*] ↑ Total LTM (1.34 kg, 95% CI 0.34-2.3)[*]
Kobashigawa et al. (1999)[RCT]	Sit-to-stand within 1 minute	↑ Sit-to-stand rate (+13.3 no./min)[*]
Wu et al. (2008)[RCT]	Isokinetic dynamometer	↑ Fatigue index (+8.8 ± 10.5%)[*] ↔ Isometric maximal strength of quadriceps[**]
	Sit-to-stand within 1 minute	↑ Sit-to-stand rate (+5.1 ± 3.6 no./min)[*]
2. Cardiovascular function		
Haykowsky, Taylor, Kim, & Tymchak (2009)[RCT]	Submaximal cycle exercise echocardiographic test	↔ EDA, ESA, stroke area and area EF at rest and submaximal exercise[**]
	Brachial artery ultrasound imaging	↔ Brachial artery EDVD and EIVD[**]
Rustad, Nytrøen, Amundsen, Gullestad, & Aakhus (2014)[RCT]	Submaximal cycle exercise echocardiographic test	↔ All parameters, including EF, EDV, ESV and $\dot{Q}$ [**]
Haykowsky et al. (2005)[UCT]	Submaximal cycle exercise echocardiographic test	(1) During exercise: - ↔ EDV, ESV and $\dot{Q}$ [**] - ↑ The effective arterial elastance[*] - ↓ SV and EF[*] (2) At rest: ↔ All parameters
3. Adverse event		
Yes	-	
No	Haykowsky, Taylor, Kim, & Tymchak (2009); Kobashigawa et al. (1999); Rustad, Nytrøen, Amundsen, Gullestad, & Aakhus (2014); Wu et al. (2008); Haykowsky et al. (2005)	

[RCT] Compare training with control; [UCT] Compare post-training with baseline; ↑, increase; ↓, decrease; ↔, no change; [*] $P < .05$; [**] $P > .05$. RM, repetition maximum; EDA, end-diastolic cavity area; EDV, end-diastolic volume; EDVD, endothelial-dependent vasodilation; EF, ejection fraction; EIVD, endothelial-independent vasodilation; ESA, end-systolic cavity area; ESV, end-systolic volume; LTM, lean tissue mass; $\dot{Q}$, cardiac output; SV, stroke volume

6. Discussion

6.1 Findings

The effect of exercise-based CR on improving exercise capacity in adult HTRs has been reported by the latest Cochrane reviews (Anderson et al., 2017) but the median age of patients within trials (54.4 years) was not representative of the elderly HTRs, which are growing over time. By only including studies whose training participants were older than 55 years of age, studies in the current review demonstrated significant increased exercise capacity in elderly HTRs after undergoing exercise-based CR despite no significant improvement of cardiovascular function.

HTRs who were ≥55 years of age have been defined as elderly patients (Borkon et al., 1999; Tjang et al., 2008); therefore, study participants in this review, which had a median age of 57 years, can be defined as elderly HTRs. This median age of training participants is also more than that for adult transplants in the ISHLT Registry, i.e. 55 years (Lund et al., 2017). However, it should be noted that there were two studies that had an average age of control participants of <55 years (Kobashigawa et al., 1999; Wu et al., 2008).

After surgery, decreased exercise capacity in HTRs can result from either central (e.g. reduced $\dot{Q}$, chronotropic incompetence, pulmonary dysfunction, and systolic and diastolic dysfunction) or peripheral (e.g. reduced oxidative capacity, endothelial dysfunction, and reduced muscle mass and strength) factors (Nytrøen & Gullestad, 2013). In addition to increased $\dot{V}O_2$peak after the training period, this current review also found a significant improvement in peak workload and peak PO, which can indicate that ET improved exercise capacity in elderly HTRs. Also, increased peripheral

muscular strength, and leg and total LTM without any significant improvement in cardiopulmonary function, including exercise LV systolic function, $\dot{Q}$ and $\dot{V}_E$ were reported in some studies. Additionally, decreased SV and ejection fraction (EF) after training were also found in one UCT (Haykowsky et al., 2005).

Haykowsky et al. (2009) stated that skeletal muscle adaptations (i.e. improved skeletal morphology and oxidative enzyme activity) may lead to oxygen utilization improvement and this can result in increased exercise capacity. In this way, an increase in exercise capacity in elderly HTRs may be mainly related to such peripheral adaptations after ET. However, a significant increase in chest press strength without any improvements in latissimus dorsi pulldown and arm curl strength was insufficient evidence to determine the effects of exercise training on upper extremity muscular strength in elderly HTRs. A period of approximately 4-5 years posttransplant of participants in Haykowsky et al. (2009) may cause no significant changes in such muscle groups between the training and control groups due to a recovery after surgery.

Although no significant improved resting HR and peak HR was reported in most RCTs in this review, significant improved peak HR in the training subjects was reported in one study, which used a 1-year programme of HIIT (Rustad et al., 2014). Nytrøen et al. (2012) demonstrated that a 1-year HIIT-programme decreased resting HR, increased peak HR and increased HR reserve in HTRs compared to the controls. However, the use of a 4-week combination programme of moderate CT and HIIT in Haykowsky et al. (2009) did not result in significant change in peak HR. This means that the ≥1-year HIIT-

programme may be more effective to alleviate chronotropic incompetence in elderly HTRs.

Due to chronotropic incompetence, HR-based intensity is not appropriate for HTRs, whereas RPE is recommended (American Association of Cardiovascular and Pulmonary Rehabilitation [AACVPR], 2013; American College of Sports Medicine [ACSM], 2018; Association of Chartered Physiotherapists in Cardiac Rehabilitation [ACPICR], 2015). Moreover, 10-15 minutes of warm-up and cool-down were also important (ACPICR, 2015). In this review, training intensity of aerobic exercise was mostly based on percentages of $\dot{V}O_2$peak and RPE, while Rustad et al. (2014) used percentages of peak HR. The use of warm-up and cool-down was stated in only two studies. One reported 5 minutes of warm-up and cool-down (Wu et al., 2008) and one reported only 10 minutes of warm-up (Rustad et al., 2014). These inappropriate prescriptions might affect the validity of data outcomes.

With the exception of Rustad et al. (2014), all the studies in this review included strength training, which can counteract the adverse side effects of immunosuppressants on bone and skeletal muscle as stated in AACVPR (2013) and ACSM (2018).

A cycle ergometer was used as a testing device in the majority of studies, while one study used a treadmill for exercise testing (Rustad et al., 2014). Treadmill testing is claimed to be more suitable for subjects because people are familiar with walking (Foster, Hume, Dickinson, Chatfield, & Byrnes, 1986) and results in 11% higher maximal oxygen consumption ($\dot{V}O_2$max) than during cycling (Huggett, Connelly, & Overend, 2005). However, the use of a cycle ergometer may be more appropriate for older

adults because it is suitable for common elderly health problems, including balance deficit, as well as being easier to obtain physiological measures during exercise testing (Huggett et al., 2005). These differences of between exercise testing methods should be taken into consideration.

An increase in exercise capacity by 1 metabolic equivalent (MET) was associated with 12% increased survival in CVD patients (Myers et al., 2002). In this review, the mean increase in $\dot{V}O_2$peak after the training period ranged from 2.5-3.7 ml/kg/min as compared to the baseline in all studies and ranged from 3.2-6.0 ml/kg/min as compared to the controls within RCTs. Based on the standard MET (i.e. 1 MET = 3.5 ml/kg/min), this means that ET may lead to reduced risk of death in elderly HTRs.

It has been stated that cyclosporin, which is a commonly used immunosuppressant therapy, is associated with arterial hypertension, vasodilation impairment and endothelial cell damage (Miller, 2002). For this reason, no significant improvement of EnF, which was found in this review, may result from cyclosporin toxicity. However, Schmidt et al. (2002) revealed that improved flow-mediated vasodilation in elderly HTRs participating in aerobic training indicated that a regular exercise programme may overcome the adverse side effects of cyclosporin on vascular impairment. Due to the small size of the study by Schmidt et al. (2002) (i.e. 7 for training HTRs; 6 for sedentary HTRs; 6 for healthy controls) and the fact that in this current review only one trial assessed brachial artery EnF, there was inadequate evidence to determine the effect of exercise on EnF in elderly HTRs.

In 2017, a Cochrane review of 23 RCTs showed that the effect of home-based CR on exercise capacity was similar to that of centre-based CR for both short- and long-term

programmes (Anderson et al., 2017). In this review, while three RCTs, which were a centre-based programme, reported increased $\dot{V}O_2$peak when compared to the controls, no significant value was reported in an RCT with a home-based programme (Wu et al., 2008). However, this inconsistent result cannot be considered conclusive due to a very small number of included studies that used home-based exercise in this review (i.e. one study).

As for adverse events, although none of the included studies reported any adverse events related to the exercise programme, it should be noted that included subjects in all studies were clinically stable HTRs.

6.2 Limitations

There are a number of limitations in this review. Firstly, the small number of trials due to the limited study of elderly HTRs makes it difficult to draw definitive conclusions. Secondly, the studies were conducted over a short period (i.e. a median of 12 weeks [range 8-48]). Therefore, there was no evidence to assess the long-term effect of exercise-based CR. In terms of risk of bias in the included studies, this review included one UCT (Haykowsky et al., 2005), which was rated 3 out of 10 of a PEDro score. Although subjects in all RCTs were randomly assigned to the groups, these subjects and the staff supervising the ET were not blinded. Despite receiving a PEDro score of 5 out of 10, the study of Wu et al. (2008) was considered high risk of bias because four participants that were randomly assigned to the training group chose to participate in the control group. Additionally, this review included two trials that were from the same centre with the same lead author (Haykowsky et al., 2005; Haykowsky et al.,

2009). Finally, this current review was conducted by a single reviewer due to it being a Master's dissertation. This may have caused selection bias and a number of errors.

6.3 Further studies

Although the findings of this review have shown that exercise-based CR increases exercise capacity in elderly HTRs, this is a short-term effect of ET. Future studies should be designed to assess long-term sustainability of exercise-based CR on exercise capacity by focusing on a longer follow-up period (i.e. >1 year).

7. Conclusion

Despite there being no significant alterations of cardiovascular function, exercise-based CR can improve exercise capacity in elderly HTRs through an improvement of peripheral skeletal muscle performance. Aerobic and strength training are safe for elderly HTRs who are clinically stable. Additionally, there is a possible beneficial effect of ≥1-year HIIT on improving peak HR in elderly HTRs. The different effects of home- versus centre-based ET are uncertain due to the small number of trials. Other outcomes, including endothelial function, cannot be conclusive due to the small size of included trials. However, this review has indicated that prospective controlled trials on exercise-based CR in elderly HTRs are limited, therefore further research is needed.

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9. Appendices

Appendix A: Search terms and key words

Terms for heart transplantation	**Terms for exercise-based cardiac rehabilitation**	**Terms for exercise capacity**
Heart transplant*	Cardiac rehabilitation	Exercise capacity
Cardiac transplant*	Rehabilitation	Exercise performance
	Exercise	Physical function
	Exercise intervention	Oxygen consumption
	Exercise program	VO_2
	Exercise programme	
	Exercise training	
	Physiotherapy	
	Physical therapy	
	Physical activity	
	Training*	
	Aerobic*	
	Strength*	

Appendix B: PEDro scale and brief explanation of each item

PEDro scale

1.	eligibility criteria were specified	no ❑ yes ❑ where:
2.	subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	no ❑ yes ❑ where:
3.	allocation was concealed	no ❑ yes ❑ where:
4.	the groups were similar at baseline regarding the most important prognostic indicators	no ❑ yes ❑ where:
5.	there was blinding of all subjects	no ❑ yes ❑ where:
6.	there was blinding of all therapists who administered the therapy	no ❑ yes ❑ where:
7.	there was blinding of all assessors who measured at least one key outcome	no ❑ yes ❑ where:
8.	measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	no ❑ yes ❑ where:
9.	all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	no ❑ yes ❑ where:
10.	the results of between-group statistical comparisons are reported for at least one key outcome	no ❑ yes ❑ where:
11.	the study provides both point measures and measures of variability for at least one key outcome	no ❑ yes ❑ where:

The PEDro scale is based on the Delphi list developed by Verhagen and colleagues at the Department of Epidemiology, University of Maastricht (*Verhagen AP et al (1998). The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology, 51(12):1235-41*). The list is based on "expert consensus" not, for the most part, on empirical data. Two additional items not on the Delphi list (PEDro scale items 8 and 10) have been included in the PEDro scale. As more empirical data comes to hand it may become possible to "weight" scale items so that the PEDro score reflects the importance of individual scale items.

The purpose of the PEDro scale is to help the users of the PEDro database rapidly identify which of the known or suspected randomised clinical trials (ie RCTs or CCTs) archived on the PEDro database are likely to be internally valid (criteria 2-9), and could have sufficient statistical information to make their results interpretable (criteria 10-11). An additional criterion (criterion 1) that relates to the external validity (or "generalisability" or "applicability" of the trial) has been retained so that the Delphi list is complete, but this criterion will not be used to calculate the PEDro score reported on the PEDro web site.

The PEDro scale should not be used as a measure of the "validity" of a study's conclusions. In particular, we caution users of the PEDro scale that studies which show significant treatment effects and which score highly on the PEDro scale do not necessarily provide evidence that the treatment is clinically useful. Additional considerations include whether the treatment effect was big enough to be clinically worthwhile, whether the positive effects of the treatment outweigh its negative effects, and the cost-effectiveness of the treatment. The scale should not be used to compare the "quality" of trials performed in different areas of therapy, primarily because it is not possible to satisfy all scale items in some areas of physiotherapy practice.

Last amended June 21st, 1999

Notes on administration of the PEDro scale:

All criteria	**Points are only awarded when a criterion is clearly satisfied**. If on a literal reading of the trial report it is possible that a criterion was not satisfied, a point should not be awarded for that criterion.
Criterion 1	This criterion is satisfied if the report describes the source of subjects and a list of criteria used to determine who was eligible to participate in the study.
Criterion 2	A study is considered to have used random allocation if the report states that allocation was random. The precise method of randomisation need not be specified. Procedures such as coin-tossing and dice-rolling should be considered random. Quasi-randomisation allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.
Criterion 3	*Concealed allocation* means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criteria, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was "off-site".
Criterion 4	At a minimum, in studies of therapeutic interventions, the report must describe at least one measure of the severity of the condition being treated and at least one (different) key outcome measure at baseline. The rater must be satisfied that the groups' outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount. This criterion is satisfied even if only baseline data of study completers are presented.
Criteria 4, 7-11	*Key outcomes* are those outcomes which provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcome measure.
Criterion 5-7	*Blinding* means the person in question (subject, therapist or assessor) did not know which group the subject had been allocated to. In addition, subjects and therapists are only considered to be "blind" if it could be expected that they would have been unable to distinguish between the treatments applied to different groups. In trials in which key outcomes are self-reported (eg, visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind.
Criterion 8	This criterion is only satisfied if the report explicitly states *both* the number of subjects initially allocated to groups *and* the number of subjects from whom key outcome measures were obtained. In trials in which outcomes are measured at several points in time, a key outcome must have been measured in more than 85% of subjects at one of those points in time.
Criterion 9	An *intention to treat* analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.
Criterion 10	A *between-group* statistical comparison involves statistical comparison of one group with another. Depending on the design of the study, this may involve comparison of two or more treatments, or comparison of treatment with a control condition. The analysis may be a simple comparison of outcomes measured after the treatment was administered, or a comparison of the change in one group with the change in another (when a factorial analysis of variance has been used to analyse the data, the latter is often reported as a group × time interaction). The comparison may be in the form hypothesis testing (which provides a "p" value, describing the probability that the groups differed only by chance) or in the form of an estimate (for example, the mean or median difference, or a difference in proportions, or number needed to treat, or a relative risk or hazard ratio) and its confidence interval.
Criterion 11	A *point measure* is a measure of the size of the treatment effect. The treatment effect may be described as a difference in group outcomes, or as the outcome in (each of) all groups. *Measures of variability* include standard deviations, standard errors, confidence intervals, interquartile ranges (or other quantile ranges), and ranges. Point measures and/or measures of variability may be provided graphically (for example, SDs may be given as error bars in a Figure) as long as it is clear what is being graphed (for example, as long as it is clear whether error bars represent SDs or SEs). Where outcomes are categorical, this criterion is considered to have been met if the number of subjects in each category is given for each group.

Source: PEDro (1999)

Appendix C: Excluded studies

	Study	Reason for exclusion
1.	Bernardi, L., Radaelli, A., Passino, C., Falcone, C., Auguadro, C., Martinelli, L., . . . Finardi, G. (2007). Effects of physical training on cardiovascular control after heart transplantation. *International Journal of Cardiology*, *118*(3), 356-362. https://dx.doi.org/10.1016/j.ijcard.2006.07.032	Mean age of participants < 55 years (Mean age ± SD: training = 50 ± 3 years; control = 53 ± 4 years)
2.	Braith, R. W., Schofield, R. S., Hill, J. A., Casey, D. P., & Pierce, G. L. (2008). Exercise training attenuates progressive decline in brachial artery reactivity in heart transplant recipients. *Journal of Heart and Lung Transplantation*, *27*(1), 52-59. https://dx.doi.org/10.1016/j.healun.2007.09.032	Mean age of participants < 55 years (Mean age ± SD: training = 54.4 ± 13.1 years; control = 54.3 ± 9.5 years)
3.	Christensen, S. B., Dall, C. H., Prescott, E., Pedersen, S. S., & Gustafsson, F. (2012). A high-intensity exercise program improves exercise capacity, self-perceived health, anxiety and depression in heart transplant recipients: A randomized, controlled trial. *Journal of Heart and Lung Transplantation*, *31*(1), 106-107. https://dx.doi.org/10.1016/j.healun.2011.10.014	Mean age of participants < 55 years (Mean age ± SD: training = 53.4 ± 11.4 years; control = 47.3 ± 17.9 years)
4.	Dall, C. H., Christensen, S. B., Hermann, T., Prescott, E., & Gustafsson, F. (2010). A high-intensity exercise program improves peak VO_2 and reduces markers of systemic inflammation in cardiac transplant recipients: A randomized study. *Journal of Heart and Lung Transplantation*, *29*(2), S75-S75. https://dx.doi.org/10.1016/j.healun.2009.11.228	Full paper was not found
5.	Ehrman, J., Keteyian, S., Fedel, F., Rhoads, K., Levine, B., & Shepard, R. (1992). Ventilatory threshold after exercise training in orthotopic heart transplant recipients. *Journal of cardiopulmonary rehabilitation*, *12*(2), 126-130. Retrieved from https://journals.lww.com/jcrjournal/Abstract/1992/03010/Ventilatory_Threshold_After_Exercise_Training_in.8.aspx	Unable to access the full paper

	Study	Reason for exclusion
6.	Hermann, T. S., Dall, C. H., Christensen, S. B., Goetze, J. P., Prescott, E., & Gustafsson, F. (2011). Effect of high intensity exercise on peak oxygen uptake and endothelial function in long-term heart transplant recipients. *American Journal of Transplantation*, *11*(3), 536-541. https://dx.doi.org/10.1111/j.1600-6143.2010.03403.x	Mean age of participants < 55 years (Mean age ± SD: training = 53 ± 11 years; control = 47 ± 18 years)
7.	Kawauchi, T. S., de Almeida, P. O., Lucy, K. R., Bocchi, E. A., Feltrim, M. I. Z., & Nozawa, E. (2013). Randomized and comparative study between two intra-hospital exercise programs for heart transplant patients. *Revista Brasileira de Cirurgia Cardiovascular*, *28*(3), 338-346. http://dx.doi.org/10.5935/1678-9741.20130053	Mean age of participants < 55 years (Mean age ± SD: training = 39.0 ± 17.54 years; control = 42.0 ± 16.46 years)
8.	Keteyian, S., Shepard, R., Ehrman, J., Fedel, F., Glick, C., Rhoads, K., & Levine, T. B. (1991). Cardiovascular responses of heart transplant patients to exercise training. *Journal of Applied Physiology*, *70*(6), 2627-2631. https://dx.doi.org/10.1152/jappl.1991.70.6.2627	Mean age of participants < 55 years (Mean age ± SD: training = 44.3 ± 2.9 years; control = 49.2 ± 1.4 years)
9.	Kugler, C., Tegtbur, U., Malehsa, D., Bara, C., Strueber, M., Haverich, A., & Simon, A. (2008). Randomized rehabilitation to improve exercise capacity and HRQoL after heart transplantation. *Journal of Heart and Lung Transplantation*, *27*(2), S114-S115. https://dx.doi.org/10.1016/j.healun.2007.11.159	Full paper was not found
10.	Nytrøen, K., Rustad, L. A., Aukrust, P., Ueland, T., Hallén, J., Holm, I., . . . Gullestad, L. (2012). High-intensity interval training improves peak oxygen uptake and muscular exercise capacity in heart transplant recipients. *American Journal of Transplantation*, *12*(11), 3134-3142. https://dx.doi.org/10.1111/j.1600-6143.2012.04221.x	Mean age of participants < 55 years (Mean age ± SD: training = 48 ± 17 years; control = 53 ± 14 years)
11.	Nytrøen, K., Rustad, L. A., Erikstad, I., Aukrust, P., Ueland, T., Lekva, T., . . . Arora, S. (2013). Effect of high-intensity interval training on progression of cardiac allograft vasculopathy. *Journal of Heart and Lung Transplantation*, *32*(11), 1073-1080. https://dx.doi.org/10.1016/j.healun.2013.06.023	Mean age of participants < 55 years (Mean age ± SD: training = 51 ± 17 years; control = 53 ± 15 years)
12.	Nytrøen, K., Rustad, L. A., Holm, J., Aakhus, S., & Gullestad, L. (2012). High intensity interval training improves muscle strength and $\dot{V}_{O_2}$peak in heart transplant recipients. *Journal of Heart and Lung Transplantation*, *31*(4), S96-S97. https://dx.doi.org/10.1016/j.healun.2012.01.273	Full paper was not found

	Study	Reason for exclusion
13.	Pascoalino, L. N., Ciolac, E. G., Tavares, A. C., Castro, R. E., Ayub-Ferreira, S. M., Bacal, F., . . . Guimarães, G. V. (2015). Exercise training improves ambulatory blood pressure but not arterial stiffness in heart transplant recipients. *Journal of Heart and Lung Transplantation*, *34*(5), 693-700. https://dx.doi.org/10.1016/j.healun.2014.11.013	Mean age of participants < 55 years (Mean age ± SD: training = 45 ± 3 years; control = 45 ± 6 years)
14.	Pierce, G. L., Schofield, R. S., Casey, D. P., Hamlin, S. A., Hill, J. A., & Braith, R. W. (2008). Effects of exercise training on forearm and calf vasodilation and proinflammatory markers in recent heart transplant recipients: A pilot study. *European Journal of Cardiovascular Prevention and Rehabilitation*, *15*(1), 10-18. https://dx.doi.org/10.1097/HJR.0b013e3282f0b63b	Mean age of participants < 55 years (Mean age ± SD: training = 53.5 ± 13.6 years; control = 54.2 ± 6.4 years)
15.	Pokan, R., Von Duvillard, S. P., Ludwig, J., Rohrer, A., Hofmann, P., Wonisch, M., . . . Bachl, N. (2004). Effect of high-volume and -intensity endurance training in heart transplant recipients. *Medicine & Science in Sports & Exercise*, *36*(12), 2011-2016. https://dx.doi.org/10.1249/01.MSS.0000147630.71210.06	Mean age of participants < 55 years (Mean age ± SD: denervated HTR [training] = 49 ± 5 years; reinnervated HTR [training] = 48 ± 6 years; all endurance-trained HTR [training] = 47 ± 8 years; control = 47 ± 4 years)
16.	Rustad, L. A., Nytroen, K., Amundsen, B. H., Segers, P., Gullestad, L., & Aakhus, S. (2013). One year of high-intensity interval training improves exercise capacity, but not systemic arterial function in stable heart transplant recipients. *European Heart Journal*, *34*(Suppl. 1), 1081-1081. https://dx.doi.org/10.1093/eurheartj/eht310.P5780	Full paper was not found
17.	Tegtbur, U., Busse, M. W., Jung, K., Markofsky, A., Machold, H., Brinkmeier, U., . . . Pethig, K. (2003). Phase III rehabilitation nach herztransplantation [Phase III rehabilitation after heart transplantation]. *Zeitschrift für Kardiologie*, *92*(11), 908-915. https://dx.doi.org/10.1007/s00392-003-0968-6	Full paper was not published in English

	Study	Reason for exclusion
18.	Yardley, M., Gullestad, L., Bendz, B., Bjørkelund, E., Rolid, K., Arora, S., & Nytrøen, K. (2017). Long-term effects of high-intensity interval training in heart transplant recipients: A 5-year follow-up study of a randomized controlled trial. *Clinical Transplantation*, *31*(1). https://dx.doi.org/10.1111/ctr.12868	Mean age of participants < 55 years (Mean age ± SD: training = 47 ± 18 years; control = 52 ± 15 years)

Appendix D: Validity of included studies

Criteria (the PEDro scale)		Haykowsky, Taylor, Kim, & Tymchak (2009)	Kobashigawa et al. (1999)	Rustad, Nytrøen, Amundsen, Gullestad, & Aakhus (2014)	Wu et al. (2008)	Haykowsky et al. (2005)
1.	Eligibility criteria were specified	No	No	No	Yes	No
2.	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	1	1	1	1	0
3.	Allocation was concealed	0	1	1	0	0
4.	The groups were similar at baseline regarding the most important prognostic indicators	0	1	1	1	0
5.	There was blinding of all subjects	0	0	0	0	0
6.	There was blinding of all therapists who administered the therapy	0	0	0	0	0
7.	There was blinding of all assessors who measured at least one key outcome	0	0	1	0	0
8.	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	1	1	1	0	1
9.	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by “intention to treat”	0	0	0	1	0
10.	The results of between-group statistical comparisons are reported for at least one key outcome	1	1	1	1	1
11.	The study provides both point measures and measures of variability for at least one key outcome	1	0	1	1	1
Total score (maximum = 10)		4	5	7	5	3

Appendix E: Characteristics of included studies

Author: Haykowsky, Taylor, Kim and Tymchak (2009)

Title: Exercise training improves aerobic capacity and skeletal muscle function in heart transplant recipients

Study design	Randomised controlled trial
Validity score	PEDro scale = 4/10
Location/ Funding	Canada/ Heart and Stroke Foundation of Alberta, NWT & Nunavut
Study objectives	To examine the effects of 12-week supervised aerobic and strength training (SET) vs. no-training (NT) on aerobic capacity, submaximal exercise LV systolic function, peripheral vascular function, lean tissue mass (LTM) and maximal muscular strength in clinically stable HTRs
Participants	**Inclusion criteria:** Clinically stable HTRs after HTx ≥ 0.5 years **Exclusion criteria:** Not stated **Number of randomised participants:** 43 (training: 22; control: 21) **Age (mean ± SD):** Training: 57 ± 10 years; control: 59 ± 11 years **Time since HTx:** Training: 5.4 ± 4.9 years; control: 4.4 ± 3.3 years **Drop out/ reason** - Training: 1 (4.5%)/ 1 subject had significant coronary disease - Control: 2 (9.5%)/ 2 subjects requested not to perform the post-intervention assessments
	Notes: There was a statistically significant difference between both groups in the following baseline characteristics: - Pre-transplant ischemic heart failure (training: 45%; control: 76%, P = .04) - Body weight (training: 80 ± 22 kg; control: 93 ± 14 kg, P = .03)
Interventions	**Setting:** Centre-based exercise programme **Components:** Exercise only **Interventions:** Supervised aerobic and strength training **Total duration:** 12 weeks
Aerobic training	**Training method:** Treadmill and cycle exercise **Frequency:** - First 8 weeks: 5 days/week - Final 4 weeks: 3 days/week for continuous training; 2 days/week for interval training

Haykowsky, Taylor, Kim and Tymchak (2009): *Continued*

	Intensity: - First 8 weeks: 60-80% $\dot{V}_{O_2}$peak - Final 4 weeks: 80% $\dot{V}_{O_2}$peak for continuous training; 90-100% of baseline peak power output (PO) for interval training (cycle) **Time per session:** - First 8 weeks: 30-45 minutes - Final 4 weeks: 45 minutes for continuous training; 15-37.5 minutes for interval training (30s exercise followed by 60s rest x initially 10 repetitions and gradually increase to 25 repetitions)
Strength training	**Training method:** Chest press, latissimus dorsi pull down and arm curls for upper extremities; leg press for lower extremities **Frequency:** 2 days/week **Intensity:** 50% of maximal strength **Time per session:** 1-2 sets of 10-15 repetitions
Control group	- No training and exercise guidelines - Continue usual activities of daily living
Co-interventions	Medication such as ASA, beta blocker, azathioprine, cyclosporine and prednisone (same medication within the groups)
Outcomes	**1. Aerobic capacity** **Exercise testing method:** Electrically braked cycle ergometer **Exercise testing protocol:** Incremental cycle exercise test to the $\dot{V}_{O_2}$peak (initially set PO 15 W and increase by 15 W every 2 minutes) **2. LV systolic function** **Method:** Two-dimensional transthoracic echocardiography at rest and submaximal (25%, 50% and 75% of baseline peak PO) cycle exercise. **3. Brachial artery endothelial function** **Method:** Brachial artery ultrasound imaging **4. Maximal muscular strength** **Method:** 1-RM test (leg press; chest press; latissimus dorsi pulldown; right and left arm curls) **5. Lean tissue mass** **Method:** Imaging technique (dual energy x-ray absorptiometry)
Adverse outcomes	No adverse events

Haykowsky, Taylor, Kim and Tymchak (2009): *Continued*

Results with statistical significance	**1. Aerobic capacity** 1.1 $\dot{V}_{O_2}$peak (+3.11 ml/kg/min [95% CI 1.19-5.03], P = .003) and peak PO (+20.9 W [95% CI 11.96-29.9], P < .0001) of SET were significantly higher than that of NT (adjusted analysis) 1.2 No significant difference of changes in peak RER (0.04 [95% CI -0.02-0.10], P = .17), peak HR (6.73 bpm [95% CI -0.05-13.5], P = .06), SBP (-9.5 mmHg [95% CI -22.6-3.64], P = .17) and DBP (2.6 mmHg [95% CI -4.1-9.3], P = .46) between SET and NT (adjusted analysis) **2. LV systolic function** End-diastolic cavity area, end-systolic cavity area, stroke area and area ejection fraction at rest and submaximal (25%, 50%, 75%) cycle exercise were not significantly different in both SET and NT after training (P > .05) **3. Brachial artery endothelial function** Endothelial-dependent and -independent vasodilation were not significantly different in both SET and NT (P > .05) **4. Maximal muscular strength** Leg-press (34.7 kg, 95% CI 3.7-65.6) and chest-press strength (10.4 kg, 95% CI 5.2-15.5) were significantly higher (P < .05) in SET vs. NT with no difference in latissimus dorsi pulldown or arm curl strength (P > .05). **5. Lean tissue mass** Leg (0.78 kg, 95% CI 0.31-1.3) and total LTM (1.34 kg, 95% CI 0.34-2.3) were significantly higher in SET compared to NT (P < .05)
Conclusion	Supervised aerobic and strength training for 12 weeks results in an increase in $\dot{V}_{O_2}$peak, leg and total LTM as well as upper and lower extremity maximal strength in clinically stable HTRs without improving exercise LV systolic function or brachial artery endothelial function.
Key discussion points	The effects of 12 weeks of supervised aerobic and strength do not improve cardiovascular function in HTRs but can improve aerobic capacity through peripheral skeletal muscle adaptations, which result in increased oxygen utilization by the active muscles.

Author: Kobashigawa et al. (1999)

Title: A controlled trial of exercise rehabilitation after heart transplantation

Study design	Randomised controlled trial
Validity score	PEDro scale = 5/10
Location/ Funding	USA/ not stated
Study objectives	To assess the effect of 6-month programme of rehabilitative exercise on physical-work capacity and activities of daily living in HTRs
Participants	**Inclusion criteria:** HTRs who underwent the midatrial-cuff technique between August 1992 and June 1993 **Exclusion criteria:** Multiple medical limitations due to prolonged hospitalisation **Number of randomised participants:** 27 (training: 14; control: 13) **Age (mean ± SD):** Training: 55 ± 8 years; control: 50 ± 12 years **Time since HTx:** 2 weeks (both groups) **Drop out:** Not stated
	Notes: There were no statistically significant differences of baseline characteristics between groups, including the mean dose of prednisone, the number of rejection episodes and the number of infections.
Interventions	**Setting:** Centre-based exercise programme and some specific instructions for exercising at home **Components:** Exercise only **Interventions:** Supervised aerobic, strengthening and flexibility exercises **Total duration:** 6 months
	Notes: - Subjects in the training group received an individual supervised programme of exercise by physiotherapists according to their physical examination results - Subjects in both groups received written guidelines to be performed at home included: shoulder circles (10 times forward and 10 times backward); shoulder retraction (10 repetitions); side bends (10 times in each direction); half-squats (10-20 repetitions); toe raises (10-20 repetitions). - Subjects in both groups received written walking guidelines to be performed at home: 1st week, comfortable pace walking 5-10 minutes, 3-4 times/day 2nd week, comfortable pace walking 10-15 minutes, 3 times/day 3rd week, comfortable pace walking 15-20 minutes, 2 times/day 4th week, comfortable pace walking 20-30 minutes, 1 time/day

Kobashigawa et al. (1999): *Continued*

	5th week, comfortable pace walking 30-40 minutes, 1 time/day 6th week, walking 30-40 minutes with increasing the pace, every day
Aerobic training	**Training method:** Treadmill, bicycle or arm ergometer **Frequency:** Initially, centre-based exercise programme: 1-3 times/ week. Then, gradually reduced to 1 time/ 2 weeks (to encourage independent exercise at home) **Intensity:** Moderate intensity due to patient's tolerance **Time per session:** ≥ 30 minutes of continuous exercise
	Notes: Duration and intensity were increased to meet the individual's tolerance
Strength training	**Training method:** Closed-chain resistive activities (such as bridging, half-squats, and toe raises) and abdominal exercise **Frequency:** Similar to aerobic training **Intensity:** Not stated **Time per session:** Not stated
Flexibility training	**Training method:** Chest expansion and thoracic mobility exercises (side stretches, trunk twists, scapula squeezes and shoulder rolls) **Frequency:** Similar to aerobic training **Intensity:** Not stated **Time per session:** Not stated
Control group	Undergo unstructured exercise (receiving written exercise guidelines and participating in non-formal supervised exercise sessions after discharge from the hospital)
Co-interventions	- Triple-drug immunosuppression (cyclosporine, azathioprine, and prednisone) - Written exercise guidelines at home
Outcomes	**1. Aerobic capacity** **Exercise testing method:** Bicycle ergometry **Exercise testing protocol:** Incremental symptom-limited (initially set no workload for 3 minutes and increase by 10 W every 1 minute [keep pedalling at 50-70 rpm] until the point of $\dot{V}_{O_2}$peak) **2. Muscle strength** **Method:** Sit-to-stand within 1 minute
Adverse outcomes	No adverse events
Results with statistical significance	**1. Aerobic capacity** The training group had significantly greater improvements in following cardiopulmonary function than that in the control group.

Kobashigawa et al. (1999): *Continued*

Results with statistical significance	- $\dot{V}O_2$peak (ml/kg/min): training vs. control: +4.4 vs. +1.9, P = .01 - Workload (W): training vs. control: +35 vs. +12, P = .01 - Ventilatory equivalent for carbon dioxide: training vs. control: -13 vs. -6, P = .02 No significant difference of changes between the training and control groups in ventilatory equivalent for oxygen (-12 vs. -4, P = .09), duration of exercise (+2.1 vs. +1.1 min, P = .07), time to estimated lactic acidosis threshold (+1.5 vs. 0 min, P = .09), resting HR (+10 vs. +18 bpm, P = .06), peak HR (+23 vs. +27 bpm, P = .25), resting SBP (-5 vs. -16 mmHg, P = .20), peak SBP (+7 vs. +9 mmHg, P = .46) and minute ventilation (+7 vs. +16 L/min, P = .10) **2. Muscle strength** The increase in the sit-to-stand rate (no./min) was significantly greater in the training group than in the control group (+13.3 vs. +5.6, P = .02)
Conclusion	Early provision of a structured, individualised exercise programme improves physical work capacity in HTRs.
Key discussion points	The improvement in the lactic acidosis threshold after exercise training in this study indicates that increased physical capacity in HTRs relates to a physiologic training effect rather than the ability to perform at a greater level of exertion.

Author: Rustad, Nytrøen, Amundsen, Gullestad and Aakhus (2014)

Title: One year of high-intensity interval training improves exercise capacity, but not left ventricular function in stable heart transplant recipients: A randomised controlled trial

Study design	Randomised controlled trial
Validity score	PEDro scale = 7/10
Location/ Funding	Norway/ the Norwegian University of Science and Technology and the South-East Health Region in Norway
Study objectives	To investigate the effects of 1-year HIIT on cardiac function and exercise capacity in stable HTRs by using comprehensive rest- and exercise-echocardiography and cardiopulmonary exercise testing
Participants	**Inclusion criteria:** - Clinically stable HTRs after HTx 1-8 years with optimal medical treatment - Ability to perform maximal exercise testing - Willingness to fulfil 1-year exercise training **Exclusion criteria:** HF, signs of rejection, atrial fibrillation, need for revascularisation or other intervention **Number of randomised participants:** 52 (training: 26; control: 26) **Age (median [range]):** Training: 56 years (20-72); control: 58 years (19-71) **Time since HTx:** Training: 5 years (1-8); control: 4 years (1-7) **Drop out/ reason** - Training: 2 (7.7%)/ 1 subject had cholecystitis; 1 subject had depression - Control: 2 (7.7%)/ 1 subject had myocardial infarction; 1 subject missed baseline $\dot{V}_{O_2}$peak test
	Notes: - The training group had significant lower estimated glomerular filtration rate (eGFR) than that in the control group (P = .025) - Statistical analyses comprised 24 subjects in each group (drop out subjects were excluded)
Interventions	**Setting:** Centre-based exercise programme **Components:** Exercise only **Interventions:** Supervised aerobic training **Total duration:** 1 year

Rustad, Nytrøen, Amundsen, Gullestad and Aakhus (2014): *Continued*

Interventions	**Notes:** - The intervention was divided into three eight-week periods of exercise **-** Exercise training consisted of 10-minute warm-up and 4 x 4-minute of work with 3-minute of active pause (no stated cool-down period) - The last eight-week period was finished 1-2 weeks before follow-up.
Aerobic training	**Training method:** Treadmill (walking or running uphill) **Frequency:** 3 sessions/week **Intensity:** - Work period: 85-95% of peak HR - Active pause period: Borg scale 11–13 **Time per session:** 28 minutes (4 x 4-minute intervals, separated by 3-minute active pauses)
Strength training	No training
Control group	Requested to continue routine exercise
Co-interventions	Medication such as cyclosporine, azathioprine, corticosteroids, statin and beta blocker (no statistically significant differences between groups)
Outcomes	**1. Exercise capacity** **Exercise testing method:** Treadmill **Exercise testing protocol:** A modified treadmill walking test (maximal exercise test) until volitional fatigue (Borg score >18 and/or RER ≥1.05); after a warm up of 10 minutes, the inclination was increased by 2% every 2 minutes. **2. Cardiac function** **Exercise testing method:** Bicycle ergometry **Exercise testing protocol:** Submaximal cycle exercise echocardiographic test in the semi-supine position (begin with a workload of 25 W and increase by 25 W every 2 minutes with constant frequency of 50-65 rpm)
	Notes: - 29 subjects were included in the analyses of exercise echocardiography. Due to logistics and poor image quality, 44 subjects were performed at baseline; 39 subjects were performed at follow up; finally, those who had angle-deviation >20° in the tissue doppler images or reduced image quality during exercise were excluded.
Adverse outcomes	No adverse events

Rustad, Nytrøen, Amundsen, Gullestad and Aakhus (2014): *Continued*

Results with statistical significance	**1. Exercise capacity** The HIIT had a significant change in $\dot{V}_{O_2}$peak (P < .001) and peak HR (P = .016); no changes in RER (P = .336) when compared with the controls. **Outcomes of the HIIT group**: - $\dot{V}_{O_2}$peak (ml/kg/min): 27.7 ± 5.5 (pre) vs. 30.9 ± 5.3 (post), P ≤ .001 - Peak HR (bpm): 159 ± 14 (pre) vs. 163 ± 13 (post), P < .05 - RER: 1.07 ± 0.06 (pre) vs. 1.08 ± 0.04 (post), P > .05 **Outcomes of the control group**: - $\dot{V}_{O_2}$peak (ml/kg/min): 28.5 ± 7.0 (pre) vs. 28.0 ± 6.7 (post), P > .05 - Peak HR (bpm): 154 ± 15 (pre) vs. 154 ± 17 (post), P > .05 - RER: 1.06 ± 0.05 (pre) vs. 1.07 ± 0.05 (post), P > .05 **2. Cardiac function** Overall, there were no differences within or between groups (P > .05)
Conclusion	HIIT is feasible in HTRs which can improve exercise capacity despite no significant alterations of cardiac systolic and diastolic function. Extra-cardiac adaptations are associated with an increase in exercise capacity in this population.
Key discussion points	HIIT did not improve contractile function as well as LV filling and relaxation in stable HTRs due to different responses to aerobic exercise training between a transplanted heart and a non-transplanted heart. Cardiac and peripheral vascular limitations in HTRs include HR regulation by circulating catecholamines, impaired systolic cardiac function, impaired LV diastolic function and relaxation, the progressive increase of myocardial fibrosis and negative effects of immunosuppressive therapy, such as hypertension, dyslipidaemia, impaired endothelial function and muscle atrophy.

Author: Wu et al. (2008)

Title: Efficacy of a home-based exercise program for orthotopic heart transplant recipients

Study design	Randomised controlled trial
Validity score	PEDro scale = 5/10
Location/ Funding	Taiwan/ not stated
Study objectives	To evaluate the effects of 8 weeks of home-based exercise programme on aerobic capacity, muscular strength and endurance, and QOL in HTRs
Participants	**Inclusion criteria:** - Clinically stable HTRs after HTx > 1 year - Free from acute rejection (confirmed by endomyocardial biopsy) and allograft vasculopathy (confirmed by coronary angiography) in the recent 2 months - Free from infection or any other major illnesses that might interfere with the assessment or participation (Participants were confirmed medical clearance by the transplantation team of the National Taiwan University Hospital, Taiwan) **Exclusion criteria:** Not stated **Number of randomised participants:** 37 (training: 14; control: 23) **Age (mean ± SD):** Training: 60.6 ± 6.2 years; control: 51.6 ± 12.8 years **Time since HTx:** Training: 1.6 ± 1.8 years; control: 2.6 ± 1.9 years **Drop out/ reason** - Training: 2 (14.3%)/ 2 subjects lost to follow-up due to time restraints - Control: 4 (17.4%)/ 2 subjects had progressive renal dysfunction and anaemia; 2 subjects dropped out due to personal reasons
	Notes: - Initially, subjects were randomly assigned 18 HTRs to the training group and 19 HTRs to the control group; then, 4 subjects chose to change from the training to control group due to time restraints. - The training group was significantly older than the control group ($P < .05$)
Interventions	**Setting:** Home-based exercise programme **Components:** Exercise only **Interventions:** Prescribed aerobic and strength training **Total duration:** 8 weeks

Wu et al. (2008): *Continued*

	Notes: - Prescribed home-based exercise programme consisted of 5-minute warm-up, upper and lower extremity strengthening exercises, 25-30 minutes of aerobic exercises and 5-minute cool-down - Subjects in the training group were asked to visit the physiotherapy department for checking their exercise programmes every 1-2 weeks
Aerobic training	**Training method:** Walking and stepping exercises **Frequency:** ≥ 3 times/week **Intensity:** RPE 12-14 that is equivalent to 60-70% $\dot{V}_{O_2}$peak for walking **Time per session:** - 15-20 minutes for walking - 10 minutes for stepping
Strength training	**Training method:** - Upper extremities: arms curls, triceps extension in shoulder elevation, chest press and standing shoulder press - Lower extremities: half squats, toe raises, bridging exercise and bridging exercise with 1 straight leg rising **Frequency:** Similar to aerobic training **Intensity:** Not stated **Time per session:** Not stated
Control group	No training; keep usual activity lifestyle
Co-interventions	Immunosuppressive therapy included prednisolone, cyclosporine, azathioprine and FK506 (similar in both groups)
Outcomes	**1. Aerobic capacity** **Exercise testing method:** Electrically braked bicycle ergometer **Exercise testing protocol:** Symptom-limited maximal to exhaustion (leg fatigue, general fatigue or dyspnoea; unable to keep pedalling at a 50-60 rpm), initially set at 0 W and increase by 10 W every minute **2. Muscle strength and endurance** **Method:** - Isokinetic dynamometer (Cybex 6000) to measure isometric and isotonic contraction of the right quadriceps - Sit-to-stand movements in 1 minutes

Wu et al. (2008): *Continued*

	3. QOL **Method:** Using a brief version of the World Health Organization Questionnaire on Quality of Life (WHOQOL-BREF) **4. PA and diet calories** **Method:** A 7-day PA and a simple 24-hour unstructured diet recall questionnaire were used to evaluate daily PA and caloric intake of subjects, respectively, for every 4 weeks
Adverse outcomes	No abnormal haemodynamic responses; no major adverse events or mortality
Results with statistical significance	**1. Aerobic capacity** The training group had significantly higher difference in peak workload (W) than those in the control group (+9.7 ± 12.9 vs. -1.0 ± 7.6, P < .05) No significant changes (P > .05) between the training and the control groups: $\dot{V}O_2$peak (+1.0 ± 2.5 vs. -0.5 ± 1.8 ml/kg/min), peak HR (+1.1 ± 10.0 vs. -2.0 ± 8.7 bpm), peak minute ventilation (+2.7 ± 10.8 vs. +0.3 ± 7.7 L/min), peak RPE (+0.4 ± 1.0 vs. +0.1 ± 0.8), resting HR (-1.1 ± 5.8 vs. -1.1 ± 3.5 bpm), resting SBP (+1.3 ± 5.6 vs. +0.2 ± 9.2 mmHg) and resting DBP (-3.1 ± 7.8 vs. -1.0 ± 8.5 mmHg) **2. Muscular strength and endurance** 2.1 Fatigue index (%): Fatigue index of the training group was significantly higher than that of the control group (+8.8 ± 10.5 vs. -2.5 ± 6.6, P < .05) 2.2 Sit-to-stand rate (no./min): Sit-to-stand rate of the training group was significantly higher than that of the control group (+5.1 ± 3.6 vs. -0.4 ± 4.0, P < .05) **3. QOL** Significant difference between groups was found in the physical domain of QOL. The training group had higher scores than the control group (+0.61 ± 1.70 vs. -0.55 ± 1.27, P < .05) **4. PA and diet calories** 4.1 PA (kcal/day): a significant increase in PA was found in the training group when compared with the control group (+241.5 ± 159 vs. +44.1 ± 242, P < .05) 4.2 Dietary intake (kcal/day): No significant changes (P > .05) between the training (-37 ± 354) and the control groups (+36 ± 304) during the study period

Wu et al. (2008): *Continued*

	Notes: - Sit-to-stand rate was significantly correlated with isometric quadriceps strength measured by Cybex 6000 (r = 0.34, P < .05) - At baseline, the training group had lower sit-to-stand rate (21.1 ± 5.2 no./min) than the control group (27.0 ± 5.5 no./min), P < .05 - At post-test, despite no significant changes, an increasing trend was found in the training group
Conclusion	8-week structured home-based exercise is safe and can improve lower extremity muscular strength and endurance, peak workload and QOL (physical domain) in HTRs.
Key discussion points	- Home-based training, which depends on self-efficacy, could cause the lack of significant change in $\dot{V}O_2$peak. - Improved physical performance and exercise tolerance after training affects the perception of HTRs, leading to improved QOL in physical domain. - An increase in daily energy consumption during the training period, according to the PA questionnaire, indicates lifestyle change which is importance for the long-term benefits in HTRs.

Author: Haykowsky et al. (2005)

Title: Effect of exercise training on $\dot{V}O_2$peak and left ventricular systolic function in recent cardiac transplant recipients

Study design	Uncontrolled trial
Validity score	PEDro scale = 3/10
Location/ Funding	Canada/ not stated
Study objectives	To examined the effect of 12 weeks of combined aerobic and resistance training on aerobic capacity, LVEF, and arterial afterload in HTRs
Participants	**Inclusion criteria:** Clinically stable HTRs after HTx < 1 month **Exclusion criteria:** Not stated **Number of participants:** 18 **Age (mean ± SD):** 57 ± 6 years **Time since HTx:** < 1 month **Drop out:** Not stated
	Notes: The pre-transplant HF aetiology was ischemic cardiomyopathy (n = 11), idiopathic dilated cardiomyopathy (n = 4), hypertrophic cardiomyopathy (n = 1), sarcoidosis (n = 1), and valvular disease (n = 1)
Interventions	**Setting:** Centre-based exercise programme **Components:** Exercise only **Interventions:** Supervised aerobic and strengthening exercises **Total duration:** 12 weeks
Aerobic training	**Training method:** Treadmill and/or bicycle **Frequency:** 5 days/week **Intensity:** RPE 12-14 **Time per session:** 30-40 minutes
Strength training	**Training method:** Lower extremity resistance training **Frequency:** Not stated **Intensity:** 50% of maximal strength, progressively increased as tolerated **Time per session:** 3-5 sets of 10 repetitions
Control group	-
Co-interventions	Medication (standard post-transplant pharmacologic therapy)

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Outcomes	**1. Aerobic capacity** **Exercise testing method:** Bicycle ergometry **Exercise testing protocol:** Incremental cycle exercise test (initially set at 15 W and increased by 15 W every 2 minutes until the highest 1-minute oxygen consumption [$\dot{V}O_2$peak]) **2. Cardiac function** **Exercise testing method:** Bicycle ergometry **Exercise testing protocol:** Submaximal cycle exercise echocardiographic test (50% of baseline peak PO)
Adverse outcomes	No adverse events
Results with statistical significance	**1. Aerobic capacity** After training, there was a significant increase in: 1.1 $\dot{V}O_2$peak (ml/kg/min) - Pre- vs. post-training: approximately 14 vs. 20, P < .05 1.2 Peak PO (W) - Pre- vs. post-training: 79 ± 21 vs. 113 ± 31, P < .05 1.3 Peak HR (bpm) - Pre- vs. post-training: 109 ± 14 vs. 134 ± 15, P < .05 **2. Cardiac function** After training, - The following values during submaximal exercise were significantly lower than pre-training 2.1 SV (ml): 85 ± 22 (pre) vs. 78 ± 22 (post), P < .05 2.2 EF (%): 78 ± 7 (pre) vs. 74 ± 7 (post), P < .05 - The following values during submaximal exercise were significantly higher than pre-training 2.3 The effective arterial elastance (mmHg/ml): 1.5 ± 0.5 (pre) vs. 1.7 ± 0.6 (post), P < .05 - The following values during submaximal exercise were not significant different 2.4 EDV (ml): 108 ± 25 (pre) vs. 105 ± 28 (post), P > .05 2.5 ESV (ml): 24 ± 9 (pre) vs. 27 ± 10 (post), P > .05 2.6 $\dot{Q}$ (L/min): 8.2 ± 1.9 (pre) vs. 7.9 ± 2.4 (post), P > .05

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Conclusion	12 weeks of combined aerobic and resistance training leads to a significant increase in $\dot{V}_{O_2}$peak in HTRs despite unfavourable improvements in LV systolic function due to a decrease in SV and EF after training
Key discussion points	The elevated arterial elastance in HTRs after training indicates that HTRs have increased arterial afterload, resulting in decreased exercise SV and EF. An increase in arterial afterload may be due to immunosuppression therapy, which is associated with an increase in peripheral vascular resistance; also, pre-transplant deconditioning or the detrimental effects of CHF on peripheral vascular function may result in increased arterial afterload.